

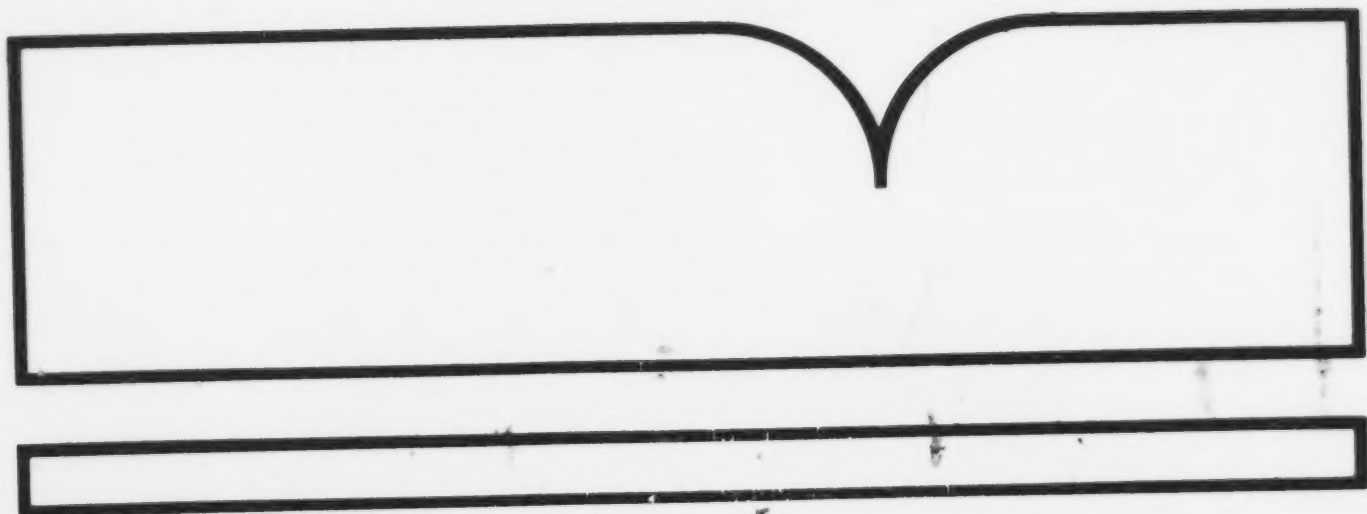
Behavioral Effects of Moderate Lead
Exposure in Children and Animal Models
Part 1: Clinical Studies

Cincinnati Univ., OH

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BEHAVIORAL EFFECTS OF MODERATE LEAD EXPOSURE IN
CHILDREN AND ANIMAL MODELS:
PART I, CLINICAL STUDIES

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I. SCOPE AND ORGANIZATION OF REVIEW

It is apparent that high-level lead exposure can have serious effects on the intellectual and behavioral development of young children. Furthermore, substantial numbers of children are at risk for lead exposure. However, current concerns revolve more around low-level chronic exposure than around high-level lead poisoning. Of particular concern are issues of quantification of behavioral toxicity, dose-response parameters associated with toxicity, and critical periods of exposure; i.e., what types of behavioral or intellectual deficits occur at what levels of lead exposure during various stages of development. The present review attempts to organize the very large human and animal behavioral literature which has evolved during the past 10 to 15 years.

The review is organized into two major sections: Part 1, a clinical review which will examine only those studies relevant to the issue of behavioral effects resulting from relatively low-level chronic exposure, and Part 2, a review of animal studies which will focus on behavioral reports only; i.e., studies where the dependent variable is learning, performance, or some aspect of locomotor behavior. No attempt will be made to review the equally large animal literature dealing with physical development, neurochemical, electrophysiological, or neuropathological endpoints of toxicity.

II. BACKGROUND

A. Incidence

It has been known since ancient times that lead can cause poisoning in man.¹ Only within this century, however, have extensive studies of the problem been made. Thomas and Blackfan in 1914² were among the first to point out, in the American pediatric literature, the frequency of occurrence of lead encephalopathy in children.

Subsequent epidemiologic studies of lead exposure in children have consisted essentially of data compiled from case reports presenting at hospitals^{3,7} and attempts to reach out into the community via door-to-door surveys. Initially surveys focused on inner city neighborhoods.⁸⁻¹² Later, children from both urban areas¹³ and areas outside of recognized urban lead belts¹⁴ were studied. The early epidemiologic reports^{3,7} showed that children between 1 and 4 years of age comprised 90% of the clinical cases of lead poisoning. A similar proportion resided in inner city neighborhoods where the dwellings were mainly dilapidated, submarginal apartments with old, lead-containing paint that had been allowed to crumble and peel away. On the basis of these reports,^{3,7} it became axiomatic that elevated blood lead levels were confined to decaying inner cities of major metropolitan areas — the so-called "lead belts". The Surgeon General¹⁵ estimated in 1970 that 200,000 to 400,000 children across the nation might have elevated blood-lead levels, i.e., levels greater than 40 μg of lead per 100 ml of blood or 40 $\mu\text{g}/\text{dl}$. Of these, 1% (2000 to 4000) were said to suffer brain damage and an estimated 200 deaths (0.1%) occurred each year as the result of the effects of lead poisoning. Published clinical reports make it evident that lead poisoning of children living in substandard housing is still a major public health problem. However, the true size of the problem is largely unknown because many cases do not come to the attention of the medical profession.

Inner city neighborhood door-to-door surveys⁸⁻¹² and mass screening have demonstrated the ability to discover children with incipient lead intoxication before they reach symptomatic stages. Blanksma and co-workers⁸ found that blood-lead determinations performed on 68,744 slum area children revealed that 3965 (5.7%) had blood-lead values in excess of 40 $\mu\text{g}/\text{dl}$. More recently, 7.4% of 380,496 children screened during 1977 had blood-lead levels greater than 30 $\mu\text{g}/\text{dl}$, and 2.4% had blood-lead levels greater than 50 $\mu\text{g}/\text{dl}$.¹²

Conspicuous by its absence in the early literature was the basic issue of whether elevated blood-lead levels and cases of lead poisoning might occur in areas outside of recognized urban lead belts. In seeking an answer to this question, Fine et al.¹⁴ undertook the nation's first state-wide program to assess the extent of elevated blood lead levels of children in communities of intermediate population in the state of Illinois. Blood specimens were obtained from 6151 children, ages 1 to 6 years, who resided in 14 cities with 10,000 to 150,000 population. Overall, 61.4% of the total population 1 to 6 years old were tested. The mean blood-lead levels ranged from a low of 19.8 $\mu\text{g}/\text{dl}$ in Rockford to a high of 32.9 $\mu\text{g}/\text{dl}$ in Peoria, with the mean blood-lead level of the total screened population determined to be 25.5 $\mu\text{g}/\text{dl}$. For all cities screened, the number and percent of children with blood-lead values greater than 40 $\mu\text{g}/\text{dl}$ were found to be 1147 and 18.6%, respectively. Fifty-one children (0.8%) were found to have blood lead values of 80 $\mu\text{g}/\text{dl}$ or greater.

Findings of elevated blood-lead levels in nonurban children focused attention on the pervasive nature of lead exposure. The Surgeon General's estimate¹⁵ and that of Oberly¹⁷ were based upon the previously accepted hypothesis that elevated blood levels are confined to major metropolitan areas. The mass screening studies of the past 7 years in urban and nonmetropolitan children¹⁴ indicate that these estimates might require upward revision.

B. Lead Encephalopathy

The clinical picture of lead encephalitis was described in the landmark studies by Tanquerel des Planches in 1839²¹ who offered the clinical term "lead encephalopathy". A clinical estimate of permanent neurological effects of postencephalopathic lead poisoning in 425 children between the ages of 9 months and 8 years has been reported by Perlstein and Attala.²³ They reported neurological sequelae in about 30% of those

children presenting symptoms referable to the G.I. tract. Of children with encephalopathy, 80% experienced some permanent neurological deficits. Recurrent seizures and mental retardation were frequent and severe and many of these patients remained profoundly retarded. Smith et al.^{24,25} likewise report that at least 25% of the young children who survive an attack of acute lead encephalopathy sustain permanent brain damage. Subtle neurologic deficits and mental impairment were most common.

In a frequently quoted 1943 study, Byers and Lord²⁶ examined the deleterious effects of lead poisoning on the growth and development of the nervous system of young children. They followed 20 children with varying degrees of "mild encephalopathy" 8 years after they had been hospitalized and treated for lead poisoning. Though none of them had acute encephalopathy and all were considered to have made complete recovery by the time of discharge 8 years later, only one of the 20 made satisfactory progress at school. At the time of testing, the age range was from 6 years, 6 months to 15 years, with a median of 7 years, 7 months. Byers and Lord found that 19 of 20 (95%) were educationally retarded and gave evidence of intellectual and emotional difficulties, with major deficits in perceptual-motor function. The authors concluded that increased lead in the circulation of a developing infant impairs the growth and development of the central nervous system (CNS). Unfortunately, the amount of increased lead absorption was poorly documented by Byers and Lord, making quantitative correlations impossible.

Although this study is considered a landmark relative to the use of psychometric testing in lead-afflicted children, serious criticism may be leveled due to their failure to employ a control group and failure to take into account such variables as socioeconomic status and race. These variables are important because many intelligence tests, by nature of their construction and intent, are normed for a particular segment of society.²⁷ One of the most difficult criticisms to overcome is the lack of objective information on the children's behavioral and intellectual functioning prior to exposure to lead. Did the lead poisoning result in psychological deficits or did mental deficits encourage lead consumption?

C. Asymptomatic and Subencephalopathic Toxicity

More recently some investigators^{28,29,30} have speculated that varying degrees of cerebral damage may also occur in association with less severe exposures to lead, i.e., in the absence of encephalopathy. Essentially it has been argued that neurological damage increases with tissue lead concentration and that this is a progressive rather than an all-or-none phenomenon. Such reasoning inevitably leads to the following question: does excessive lead burden during the period of CNS maturation affect the intellectual and behavioral development of children when the burden is not associated with overt clinical signs of neurotoxicity?

III. CLINICAL STUDIES

Lead exposure appears to be a pervasive fact of life in many large metropolitan areas of this country. This especially seems to be the case in older urban sections of midwestern and eastern cities which are disproportionately populated by the economically disadvantaged segments of our society. The threat posed by lead to the health of the young child who is exposed to toxic levels of this substance has been known and documented over the last 30 to 40 years. Lead poisoning in children, in its most overt and dramatic form, causes encephalopathy manifested by mental confusion, convulsions, and sometimes death. Unfortunately, the early signs of such poisoning, e.g., excessive fatigue, lethargy, vomiting, and nonspecific G.I. complaints, are much more subtle than those of overt encephalopathy and often go unnoticed because they mimic

a host of other nonspecific illnesses that are common to young children. In either case, however, the outcome of such poisoning is frequently irreparable behavioral and intellectual deficiencies stemming from damage done by lead to the child's CNS. A number of followup studies on such children^{23,24} have shown high rates of morbidity as sequelae to lead poisoning. An early study by Byers and Lord²⁵ reported lowered intellectual functioning with all but 1 child out of the 20 showing poor school performance. Evidence of perceptual and perceptual-motor problems were evidenced by all the children in the sample. Impulsiveness and short attention span also appeared to be a common characteristic of these children. Later studies on this problem have shown even more dramatic forms of sequelae to lead poisoning. Perlstein and Attala,²³ for example, conducted a followup study on 425 children who had some form of lead poisoning. They found that almost 40% of these children exhibited some degree of morbidity. The most common sequela was mental retardation which occurred in 22% of these subjects. The degree of mental retardation was typically profound. When more "minor" learning blocks occurred, these appeared to be caused by deficits in visual perception. Seizures were found to be another common sequelae of lead poisoning. They occurred in 20% of the children showing some kind of morbidity, with grand mal seizures being the most frequent pattern. Other sequelae included cerebral palsy (2%) and atrophy of the optic nerve (1%). When the onset of plumbism was marked by encephalopathy (about 15% of such cases), sequelae were present, mainly in the form of mental retardation and/or seizures, in 82% of the cases.

Knowledge about the effects of lead poisoning have given rise to a nationwide effort aimed at its prevention. This has primarily taken the form of mounting programs in numerous high-risk urban areas aimed at screening infants and young children for potentially toxic levels of lead. Those children with blood-lead levels above 80 $\mu\text{g}/\text{dl}$ whole blood are frequently treated with chelating drugs. However, many authorities in the last decade have raised the question as to whether prolonged exposure to lead at levels below that deemed to be poisonous might cause less obvious forms of CNS damage which nevertheless seriously undermine the intellectual and behavioral integrity of the child. In some ways this, if it turns out to be true, could pose a health hazard to many more young children because many more such children are apparently exposed to lead at this level than are exposed to lead at levels considered to be indicative of overt toxicity.

This issue has spawned a number of recent scientific investigations aimed at discovering whether or not there are neurobehavioral effects of lead present at levels below the threshold considered to be poisonous. This is the problem often referred to as asymptomatic lead poisoning. It is this literature, which has arisen during the last 8 to 10 years, that will be reviewed. The review will focus only on those studies which have sought to determine if there is a relationship between moderate levels of lead exposure — the definition of which, we will see, varies widely from one study to the next — and behavioral deficits in children. The review will open with a brief description of the tests that are commonly used in these studies to assess intelligence and behavior followed by a critical review of each significant study in the literature. The reader will then be offered an extensive discussion of the state-of-the-art and a set of recommendations regarding the way in which future research might address this question.

A. Review of Basic Methods of Behavioral Assessment

Behavioral measures employed in these studies vary widely. They include IQ tests, measures of perceptual motor functioning, ratings of hyperactivity and behavior, and the use of school records as measures of behavior and achievement. Only those tests which have been frequently used in this literature will be described so as to give the reader some familiarity with them as he reads the review to follow.

Typically, psychometric tests have been used to measure the intelligence of lead exposed children. These tests are distinguished by the careful attention given to standardizing the items (including the directions for administration) on samples of children representative of those for whom the test has been developed. In addition, the same careful attention is paid to developing appropriate age norms for the test and for insuring that the instrument is reliable (i.e., that the scores on successive administrations of the test to the same child are statistically equivalent) and valid (i.e., that the test correlates well with other established measures of intelligence and that it predicts later functioning, typically academic performance).

The Bayley Scales of Infant Development are almost universally used to assess intellectual development during infancy (0 to 30 months). This test is composed of both a mental and a motor scale. The items on each scale have been pretested and placed in order of increasing difficulty. The infant earns a score on each scale depending on the number of items that are passed. The mental scale yields a Mental Development Index that has a mean of 100 and a standard deviation (S.D.) of 16. The motor scale yields a Psychomotor Development Index with the same mean and S.D. Items found on the mental scale test the infant's responsiveness to environmental stimulation (e.g., turning head toward the sound of a bell and tracking a red ring in an 180° arc), manipulatory skills (e.g., picking up a pellet), perceptual motor skills (e.g., the speed of putting the pegs in a pegboard), and language skills (e.g., identifying pictures of objects and understanding prepositions, etc.). The motor scale is similarly constructed with groups of items assessing the development of abilities in the areas of trunk control (e.g., rolling over and sitting without support), reaching and grasping, and locomotion. The Bayley Scales have a reasonable degree of reliability. However, their predictive validity is doubtful, as is usually the case with infant intelligence tests. This is because infants are much more variable in their moods, responsiveness, and motivation to perform in the prescribed manner on such tests. Poor validity also occurs because the nature of the items on such tests is primarily sensorimotor and thus differs greatly from the more verbally based items found on intelligence tests geared for school-age children or for adults.

In children above the age of two, the Stanford-Binet and the Wechsler series (either the Wechsler Preschool and Primary Scale of Intelligence — WPPSI — or the Wechsler Intelligence Scale for Children — WISC) have often been used to assess intelligence. The Binet is primarily an age scale. That is, a particular item is placed at a given age level where 50 to 75% of children of that age pass the item. This procedure is used to group items into age levels. In this case, six items appear at each age level. These age levels come at 6-month intervals starting at the 2-year level (the "floor" level of the test) and continuing through to the 4-year level. Above age 4, items (again six at each age level) are clustered at yearly intervals up through adulthood. Items at the early ages are mostly sensorimotor (building a tower of blocks, stringing beads, discriminating shapes, etc.) with a small mix of verbal items (e.g., identifying pictured objects and defining simple words like "ball"). Around ages 4 or 5 the mix of these items becomes mostly verbal and taps the child's skills in vocabulary, verbal reasoning, arithmetic and numerical reasoning, and verbal problem solving. Typically, this test is administered beginning at an age level where the child passes all of the items and continuing up through successive age levels until the child reaches a level where none of the items are passed. The child earns so many months credit for items passed above the basal age, i.e., the last age at which all items are passed. These months are totalled to yield a mental age. If the child is normal, the mental age should be fairly equivalent to his or her chronological age. The IQ is determined from a set of norms based on the relationship between the child's mental and chronological age. Any score between

85 and 115 is considered to be average. Scores below 85 denote some degree of subnormality. Those above 115 indicate some degree of exceptional intelligence.

The distinguishing feature of the Wechsler tests is that the instruments are divided into two scales: verbal and performance. Each scale is composed of a set of five subtests. On the verbal scale the subtests include information (e.g., "Who discovered America?"), similarities (e.g., "How are an orange and a banana alike?"), arithmetic, vocabulary (defining words), and comprehension (e.g., "What is the thing to do if a child smaller than you starts to fight with you?"). The performance scale includes subtests tapping nonverbal intellectual skills. These subtests are picture completion (picking out the missing detail in a picture), picture arrangement (arranging a series of pictures in an order that tells a story), block designs (copying pictured designs with multicolored blocks), object assembly (putting together puzzles), and coding (placing a code mark that goes with each number in a series of scrambled numbers). The subtests on the WPPSI and the WISC are generally the same, but those on the WISC reach a higher level of difficulty since they are geared for children between 6 and 16, whereas the WPPSI is geared for the 4½- to 6-year-old child. The same subtests are always administered regardless of the age of the child. The child's IQ is based on his raw scores on these subtests. In this case, three IQ scores are generated: a verbal, a performance, and a full scale or total IQ. The range of scores for below normal, normal, and above normal intelligence are much the same as that described for the Bayley and the Binet. Discrepancies between the performance IQ and the verbal IQ, especially if the performance score is 10 or more points lower, are felt to be diagnostic of possible CNS involvement. The Wechsler tests, like the Binet, show a very high degree of reliability and validity.

The McCarthy Scales of Children's Abilities (McSCA) is a measure of intelligence for use with children between the ages of 36 to 60 months. On the McSCA, separate scales measure the cognitive, quantitative, verbal, memory, perceptual-performance, and motor skills of the child. In addition, the McSCA yields an overall index of cognitive functioning — the General Cognitive Index (GCI) — which can be interpreted in much the same manner as the IQ score from the Binet or from the WISC. The McSCA is a well-standardized instrument that has a reasonable degree of reliability. In addition, the GCI correlates reasonably well with the IQs from other recognized intelligence tests (0.71 with full-scale WISC IQ and 0.81 with Binet IQ).

The Bender-Gestalt, Beery Visual Motor Integration Test (VMI), and the Harris Draw-A-Person (DAP) have been frequently used in these studies to assess perceptual-motor functioning. The first two of these tests asks the child to copy geometric figures. The quality of his/her drawings are then assessed according to how well they match the originals. The norms for both of these tests are well established and the tests appear to have a reasonable degree of reliability. They are often used as tools to diagnose brain damage, and in the hands of a skilled clinician they do an adequate job in this regard. Their value for assessing perceptual-motor immaturity is probably better established. The DAP merely asks the child to draw a picture of a man or a woman, or both. Age norms are available. This test is used to assess perceptual-motor integrity and is used sometimes as a complementary measure of intelligence.

Rating scales, such as the Wherry-Weiss-Peters Activity Scale (WWP)¹¹ and a similar scale developed by Conners,¹² have often been used in these studies to assess activity level and personal-social functioning. The WWP asks the rater, usually a parent, to rate the child's activity level on behaviors occurring during mealtime (e.g., up and down at table; interrupts without regard), while watching television or doing homework, at play, while asleep, while at school, or while away from home. Each behavioral item is rated on a three-point scale as to how often the behavior occurs, i.e., "none", "some", "much".

The scale developed by Conners³² is for use primarily by teachers. In this case, the teacher rates each of 39 items (e.g., "sits fiddling with small objects", "lies", "has temper outbursts", "is submissive") by rating the child on a four-point scale running from seldom to frequent. This scale was designed to measure behavior problems and activity level. The "hyperactive dimension" is just one of several dimensions (e.g., aggression, withdrawal) that are measured. Research on both of these scales indicates an adequate degree of reliability. Studies also indicate they may measure hyperactivity, although how pure of a measure they are is open to question. This latter problem may be in part a function of our confusion over a precise definition of hyperactive behavior.

Other less well-specified scales tapping personal-emotional status have been used, e.g., a protocol developed by the Collaborative Study on Strokes and other Neurological Diseases of Childhood. A few studies utilized grades and teachers' written ratings of the behavior of the child. These are very subjective measures of behavior with unknown reliability and validity.

In this brief review of methods of behavioral assessment, it should be pointed out that alternative measures exist and might be considered in future studies. Assessment of cognitive function and behavioral development in children under 5 years of age is difficult at best. However, during the last decade, several new assessment procedures have appeared and attempts made to apply these largely experimental methodologies to the task of detecting CNS damage. Examples of such procedures, applied largely to children under 2 years of age, are measures of orientation and habituation to external stimuli, developing visual perceptual preferences, and formation of visual recognition memory.

Many psychologists feel that the orienting reflex (OR) signals the infant's ability to direct his attention toward stimulus input. Habituation is felt to be the infant's ability to process information contained in the stimulus input to the point where it becomes stored in short-term memory. Psychophysiological measures, e.g., heart-rate acceleration and deceleration, and galvanic skin resistance and conductance, are typically used to measure OR and habituation. In the case where heart rate is used as the dependent measure, the orienting reflex would be indicated either by an acceleration or a deceleration of the heart rate with the onset of the stimulus. Habituation, on the other hand, would be signaled by a decline in the magnitude of the heart-rate changes with repeated presentations of the same stimulus. It appears that both the OR and the speed with which infants and young children habituate are possible indicators of early CNS integrity. For example, slow habituation has been found in infants with a frank history of severe malnutrition,³³ in infants with anencephaly,³⁴ and in older children diagnosed as mentally retarded.³⁵

Visual preferences, on the other hand, are measures of perceptual development. Preferences are measured by exposing the infant to two visual targets which differ on a given stimulus dimension like brightness contrast or contour density. A determination is then made of which of the two targets is looked at the longest by the infant. Fantz et al.³⁶ have shown that the stimulus dimensions that control the nature of these preferences systematically change with age. Furthermore, evidence has accrued showing that the visual preference measure may be an early detector of CNS insult. For example, Down's Syndrome infants and premature infants who later evidence some degree of mental retardation show early lags and aberrations in the development of these preferences.^{37, 38}

Measures of visual recognition memory in infants capitalize on the fact that infants prefer to look at a novel stimulus if it is paired with a stimulus that they have already looked at it for a long period of time. This is called a novelty preference. It is felt that the infant could not show a strong preference for the novel stimulus unless he or she was able to store, in short term memory, some representation of the previously exposed

familiar stimulus. Visual recognition memory is tested, then, by exposing the infant to two identical visual stimuli for a set length of time. After this the infant is presented the "familiar" stimulus paired with a novel stimulus. If the infant "remembers" seeing the familiar stimulus, he or she will typically look at the novel stimulus for a significantly greater length of time. Testing in this manner has resulted in the accumulation of evidence showing the presence of delays in the development of memory capacity in infants with suspected CNS deficits such as Down's Syndrome infants or premature infants who later evidence some degree of developmental handicap and/or mental retardation.^{38,39}

Definitive measures of the neurobehavioral status of children between the ages of 2 and 5 years are more difficult to find. However, there are measures which are potential candidates to be included in a neurobehavioral assessment battery for this age range. The measures of OR and habituation can and have been used with children throughout this age span and might prove useful in this regard. Likewise, measures of learning capacity might be adopted. They might be used to assess the child's ability to make simple associations by using measures of the rate of conditioning in either a classical or operant conditioning paradigm. Likewise, discrimination learning tasks (e.g., where the child has to learn to consistently choose the triangular object over one shaped like a square) might be a suitable alternative measure of the child's developing perceptual, perceptual-cognitive, and problem solving capacities. Uzgiris-Hunt Scales⁴¹ offer another alternative measure of cognition which might prove useful because of their heavy reliance on the child's developing perceptual and memory capacity. These scales measure sensorimotor intelligence, e.g., perception of spatial relations and awareness of cause and effect relationships based on Piagetian theory.

The one major gap in assessment at this age is a good index of the developing fine and gross motor skills. The Motor Scale from the Bayley is helpful to some extent, but it tends to measure a broad range of abilities rather than offering an in-depth assessment of one skill (e.g., hand use). However, there are some pioneering studies in this field which might eventually lead to in-depth measures in this area.⁴²

Fortunately, neurobehavioral measures do exist for children who are 5 years of age or older. Perhaps the tool *par excellence* that might be used to assess the neurobehavioral status of children between the ages of 5 and 8 years is the Indiana-Reitan Neuropsychological Test Battery.⁴³ This is a comprehensive test battery. Included in it are perceptual measures in separate sensory modalities, measures of motor performance (e.g., strength of grip and finger tapping), measures of visual-motor functioning (e.g., drawing geometric figures), measures of tactual-motor skills (e.g., putting various shaped blocks in the correctly shaped recesses while blindfolded), and measures of language skills. More than one test is given in a specific area of functioning. Furthermore, laterality of functioning is often assessed by giving some tests using first one side of the body and then the other side. In addition, the WISC is given both as a measure of intelligence and as a partial measure of specific skills that might be disrupted by brain damage. Abundant research has been done on this battery and indicates that it is useful in determining the presence, location, and extent of brain damage in children of this age. As such, it might be an excellent device in assessing whether or not moderate lead exposure leads to brain damage, as well as providing information regarding the location and extent of such damage.

B. Review of Recent Studies

1. Critical Review of Studies

The studies reviewed in this section differ widely in matters of subject selection, design, and methodology as is apparent in Table I. The diversity is so great that it is difficult to group them in any coherent manner. The authors have chosen to impose some order by grouping studies according to the way in which the investigator(s) ini-

tially identified children whom they planned to examine. In this case, studies are grouped in the following manner: (1) lead-exposed subjects identified by indices of exposure obtained concurrently with behavioral testing; (2) lead-exposed subjects identified on the basis of indices of exposure available prior to the behavioral testing, i.e., prior lead screening; (3) subjects identified on the basis of their contact with a presumed source of lead exposure, e.g., pica, airborne lead, lead in water; and (4) subjects identified on the basis of a current disorder such as mental retardation, hyperactivity, or learning disability.

The review of clinical studies has been subdivided to assist the reader. The first section provides a brief overview of those methods of behavioral assessment which have been used to quantitate lead effects. This section should prove useful to those readers not already familiar with behavioral assessment techniques. The second section contains an individual review of each study in the area. Attention has been paid to analysis of the various study designs, selection of study and control subjects, documentation of exposure history, evaluation of the neuropsychological test batteries used, and statistical treatment of the data. The reader should be aware that our discussion of documentation of lead exposure histories will focus almost exclusively on blood-lead levels. This is not to say that other methods, e.g., tooth or hair lead concentrations or "lead lines", are invalid indices. However, blood-lead values are best understood by the largest audience and therefore provide a useful common frame of reference for this diverse group of studies. It is not necessary that these reviews be read sequentially. Each critique is independent of preceding or subsequent studies. The third section provides a general overview of procedural problems common to this area of research. Individual studies are cited to illustrate various points. The reader may choose to read this overview prior to reading individual critiques. The last section provides our general conclusions regarding the effects of moderate lead exposure on the neurobehavioral development of children in light of the literature reviewed. This section also includes recommendations regarding design considerations for future studies.

a. Exposure Index Obtained Concurrent with Behavioral Testing

(1.) Kotok*

Subjects in this study were 24 children who had high blood leads (mean blood lead = $81 \mu\text{g/dl}$, range 58 to $137 \mu\text{g/dl}$) and 21 controls with low blood leads (mean PbB = $48 \mu\text{g/dl}$, range = 20 to $53 \mu\text{g/dl}$). All subjects were between 12 and 61 months of age at the time of the study. The birth records of the subjects were reviewed and subjects were given ratings on their birth history of 1, 2, or 3 if birth complications appeared to be absent, moderate, or severe; e.g., a rating of 3 was given for a C-section delivery because of loss of fetal heart beat. In a like manner, the mothers of these subjects were interviewed in order to gain data on the subject's social environment, e.g., family stability, kind of housing, financial resources, interpersonal relationships, history of drug abuse, preparation for child rearing. The interview data were used to evaluate the environment of each subject on a 3-point scale according to whether or not the child's home environment was rated as having significant problems, having problems common for an inner city home, or having no problems. All subjects were administered the Denver Developmental Screening Test (DDST). The DDST examines the child's functioning in each of four areas: gross motor, fine motor, language, and personal-social. There are groups of items in each of these sectors. The items in each sector are arranged by the ages that most children would be expected to pass them. A child passes or fails a given sector of the DDST depending on whether he passes items at or just below his age level. In this study the child's score in each of these sectors was calculated by determining the age level for the last item the child passed in each sector and dividing this age level by the child's chronological age. Statistical tests applied to the difference between the group means on the scores in each sector of the

Table 1
SUMMARY OF RESULTS OF HUMAN STUDIES ON NEUROBEHAVIORAL EFFECTS AT MODERATE BLOOD-LEAD LEVELS

Population studied	N/group	Age at testing (yr)	Blood lead ($\mu\text{g}/\text{dL}$)	Psychometric tests employed	Summary of results (C = control, Pb = lead)*	Levels of significance*	Ref.
New York, N.Y. (Blood lead registry)	Pb poisoned positive controls:						
	I. With encephalopathy = 3	$\bar{x} = 9.7$	Mdn = 110*	WISC	I II III IV V		52
	II. Without = 68	$\bar{x} = 9.0$	Mdn = 80*	Full-Scale IQ		I vs. V $p < 0.01$	
	Nonpoisoned			Bender Gestalt	77 96 92 104 99	III vs. V $p < 0.10$	
	Pb poisoning: III High Pb = 25				67 84 79 96 86	I vs. V $p < 0.005$	
	IV Low Pb	$\bar{x} = 9.0$	Mdn = 70*	Figure Drawing	70 91 87 93 93	I vs. V $p < 0.02$	
	High Tooth Pb = 24	$\bar{x} = 8.5$	Mdn = 55*	Purdue Pegboard	7.0 1.7 1.5 1.3 1.9		
	V Controls:						
	Low Pb	$\bar{x} = 9.7$	Mdn = 40*				
	Low Tooth Pb = 39		Mdn = 12*				
Cincinnati (Cincinnati Children's Hospital Lead Clinic)	Control = 27	$\bar{x} = 5.7$	$\bar{x} = 24.6$	WPPSI or WISC (Total IQ)	C = 89.8 Pb = 89.2	N.S.	53
	Lead = 27	$\bar{x} = 5.6$	$\bar{x} = 44.2$				
Glasgow, Scotland	Mentally Retarded = 77	$\bar{x} = 4.07$	25.4	Griffiths Mental Development Scales	Distribution of tap water — lead (log dF)		70
	Controls = 77	$\bar{x} = 4.07$	17.8		across subjects		
				Stanford-Binet IQ	Water		
				(Both tests used to categorize subjects)	lead		
					range		
					C		
					mentally retarded		
					0—39.9		
					40—79.9		
					80+		
					0		
					11		
						Mental retardation 1.7 * more probable if lead in tap water ($>800 \mu\text{g}/\text{L}$)	
Primarily Brooklyn, N.Y.	Hyperactive = 54 (no known etiology)	$\bar{x} = 7.8$	$\bar{x} = 26.2$	Conners Scale (teacher rating of hyperactivity)	Comparisons of PbB with respect to controls: pure hyperactive	$p < 0.01$	65
	Hyperactive with probable nonlead etiology = 9	$\bar{x} = 7.3$	$\bar{x} = 22.9$	WPPSI Scale (parent rating of hyperactivity), both tests used to categorize subjects	Probable non Pb Possible non Pb Pb poisoned	N.S. $p < 0.01$ $p < 0.001$	

Hyperactive with possible nonlead etiology = 11 Pb poisoned = 8 Control = 37	$\bar{x} = 7.7$ $\bar{x} = 7.3$ $\bar{x} = 7.6$	$\bar{x} = 29.9$ $\bar{x} = 41.1$ $\bar{x} = 22.2$	WWPS > 2.0 CS > 2.5 WWPS < 2.0 CS < 2.5	hyperactive nonhyperactive	
Hyperactive = 7 (no known etiology); Hyperactive with probable nonlead etiology = 6	$\bar{x} = 8.2$ (6-10.5)	29.2 22.5	Teacher rating scale (Conners) Parent Symptom Questionnaire (Conners) Hyperactivity Checklist (Werry)	Improvement following chelation	67
Hyperactive = 41 (no known etiology) Hyperactive with possible nonlead etiology = 12 Hyperactive with probable nonlead etiology = 31	$\bar{x} = 8.1$ $\bar{x} = 7.3$ $\bar{x} = 8.9$	24.7 26.3 20.3	Teacher rating scale (Conners) Hyperactivity check- list (Werry), both tests used to cate- gorize subjects	Etiologic group	66
Mentally retarded etiol- ogy unknown = 31 Probable cause = 33 Neuroretarded pediatric controls = 30	$\bar{x} = 7.4$ $\bar{x} = 7.3$ $\bar{x} = 7.9$	$\bar{x} = 25.5$ $\bar{x} = 18.7$ $\bar{x} = 18.8$	Standardized IQ test results used to match groups	Control vs. PbB levels	63
Control = 72 Lead = 70 Control = 67 Lead = 70	4 4 7 7	Not assayed* 40-100* See above See above	Stanford-Binet IQ Other measures WISC Full-Scale IQ Neurologic exam Other measures WISC	C = 94 Pb = 89 C > Pb on 3.4 tests C = 90 Pb = 87 C better than Pb C > Pb on 9/10 tests p < 0.05 p < 0.01 p < 0.01 p < 0.01 p < 0.001	55 57
New York (Kings county - Down- state Medical Cen- ter complex)					
Inner city (Rich- mond) Follow-up, same subjects					

Table 1 (continued)
SUMMARY OF RESULTS OF HUMAN STUDIES ON NEUROBEHAVIORAL EFFECTS AT MODERATE BLOOD-LEAD LEVELS

Population studied	N/group	Age at testing (yr)	Blood lead ($\mu\text{g}/\text{dL}$)	Psychometric tests employed	Summary of results (C = control, Pb = lead)	Levels of significance ^a	Ref.
Smelter area, Idaho	Control = 54	$\bar{x} = 7.3$	$\bar{x} = 27.9$	Verbal IQ	C = 93.3	Pb = 92.0	N.S.
	Pb = 54	$\bar{x} = 7.3$	$\bar{x} = 61.5$	Performance IQ	C = 98.7	Pb = 97.2	N.S.
	Rematched control = 50	$\bar{x} = 7.4$	$\bar{x} = 30.2$	Full Scale IQ	C = 95.5	Pb = 93.9	N.S.
				WISC	C = 96.4	Pb = 91.9	p = 0.04
Inner city (New Haven)	Rematched Pb = 20	$\bar{x} = 7.3$	$\bar{x} = 58.9$	Verbal IQ	C = 100.9	Pb = 95.9	p = 0.037
	Control = 25	3.1—5.5 ($\bar{x} = 2.7$)	20—55	Performance IQ	C = 98.4	Pb = 93.2	p = 0.01
	Lead = 24	1.0—5.8 ($\bar{x} = 2.8$)	58—137	Full Scale IQ	C = 98.4	Pb = 93.2	p = 0.01
Inner city (Rochester)	Control = 36	1.9—5.6 ($\bar{x} = 3.6$)	11—40	Denver Developmental Scale	C > Pb on 11 Sectors		44
	Lead = 31	1.7—5.4 ($\bar{x} = 3.6$)	61—200	IQE for six ability classes	IQ Equivalent for each class		48
				Social maturity	C = 126	Pb = 124	0.05 < p < 0.10 for spatial
Smelter area (El Paso)	Control = 46	3—15 ($\bar{x} = 9.3$)	<40	Spatial relations	C = 101	Pb = 92	p < 0.10 for all other ability classes
	Lead = 78	3—15 ($\bar{x} = 8.3$)	40—68	Spoken vocab., info. comprehension, Visual attention, Auditory memory	C = 93	Pb = 92	
				WISC Full Scale IQ	C = 93	Pb = 89	N.S.
				WPPSI Full Scale IQ	C = 91	Pb = 86	N.S.
				WISC + WPPSI combined	C = 93	Pb = 88	p < 0.01
				WISC + WPPSI subscales			
				Neurologic testing	C > Pb on 13, 14 scales		p < 0.01
				WISC	C > Pb on 4, 4 tests		p < 0.001
				WAIS	C = 100		N.S.
				McCarthy General Cognitive Scale IQ	Pb = 101—105		
Inner city (London)	Control = 172	6—16	<40		C = 82	Pb = 81	N.S.
Smelter area (El Paso)	Lead = 43	6—16	40—60 +		C = 89	Pb = 87	N.S.
	Control = 26—101	0.9—18 (Median = 9)	<40				61
	Lead = 26—101	0.9—18 (Median = 9)	>40				

First and second graders from Chelsea and Somerville, Mass.	Low tooth lead ($\bar{x} < 10$ ppm) = 100 High tooth lead ($\bar{x} > 20$ ppm) = 58	— —	23.8 (N = 58) 35.5 (N = 23)	Oseretsky Motor Level	C = 101	Pb = 97	N.S.	51b
				California Personality	C = 80	Pb = 72	N.S.	
				Frosting Perceptual Quotient	C = 100	Pb = 102	N.S.	
				Finger-Thumb Opposition	C = 27	Pb = 29	N.S.	
				WISC (Revised)				
				Full Scale IQ	C = 106.6	Pb = 102.4	p = 0.03	
				Verbal	C = 103.9	Pb = 99.3	p = 0.03	
				Performance	C = 108.7	Pb = 104.9	p = 0.08	
				Seashore Rhythm test (sum)	C = 21.6	Pb = 19.4	p = 0.002	
				Token test (sum)	C = 24.8	Pb = 23.6	p = 0.09	
Inner city (New York)	Control = 50 Lead = 30	3-6 3-6	10-30 40-70	Sentence Repetition test	C = 12.6	Pb = 11.3	p = 0.04	49
				Reaction time delay intervals:				
				3 sec	C = 35	Pb = 37	p = 0.32	
				12 sec	C = 41	Pb = 47	p = 0.001	
				12 sec	C = 41	Pb = 48	p = 0.001	
				3 sec	C = 38	Pb = 41	p = 0.01	
				McCarthy General Cognitive	C = 90	Pb = 80	p < 0.01	
				McCarthy Subscales	C > Pb on verbal and perceptual scales		p < 0.05	
3rd and 4th grade students	Learning disabled = 31 Control = 22	$\bar{x} = 11.4$ $\bar{x} = 11.5$	23 ppm 4 ppm	Peabody Voc. Test	Normal or above average	?	p < 0.001 for non Pb content between LD	68
				Metro. Ach. Battery	Failure on 1 or more subtests	?		
				Pupil Rating Scale	Less than 67	Greater than 68	and controls	
Inner city (Boston)	Control = 58 Lead = 58	? ?	<40 >40	Stanford Binet IQ	C = ?	Pb = 86	p < 0.001	50
				Neurologic exam	C better than Pb			

Table 1 (continued)
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Population studied	N/group	Age at testing (yr)	Blood lead ($\mu\text{g}/\text{dl}$)	Psychometric tests employed	Summary of results (C = control, Pb = lead)	Levels of significance ^a	Ref.
Residents near lead battery plant, Manchester, England	Control = 23 (moderate lead) High Lead = 24	$\bar{x} = 4.7$ $\bar{x} = 4.8$	$\bar{x} = 28.2$ $\bar{x} = 44.4$	Griffiths mental development scales M. Frosting development of visual perception (Part I) Peabody Test	C = 111 Pb = 97-107 14.3 17.5 19.5 11.8 17.3 19.8	N.S. N.S. N.S. N.S.	60
Inner city (Providence, R.I.)	Control Sx = 45 Short Pb Sx = 15 Long Pb Sx = 20 Post enceph. Pb = 10	4-8 ($\bar{x} = 5.7$) 4-8 ($\bar{x} = 5.5$) 4-8 ($\bar{x} = 5.6$) 4-8 ($\bar{x} = 5.3$)	Maximum ^a $\bar{x} = 23 \pm 8$ $\bar{x} = 61 \pm 7$ $\bar{x} = 68 \pm 13$ $\bar{x} = 88 \pm 41$	McCarthy General Cognitive McCarthy Subtests Neurologic exam tating Objective neurologic tests	C = 93 L = 88 C + S > L > P on 5.5 tests L < C < S < P on ratings C < L < S < P on 3.12 tests	P vs. C, $p < 0.01$, all others N.S. P vs. C, $p < 0.01$, all others N.S. N.S. P vs. C, $p < 0.01$, all others N.S.	51
Pb screening program in high risk inner city area (city not stated)	Controls (sibship or children raised in sibship relationship) = 47 Lead exposed	$\bar{x} = 9.7$ $\bar{x} = 8.3$	<40 Range: 50-365	Berry-Bukrenica Visual Motor Integration Ravens Progressive Matrices Figure drawing Males Females WISC-WPPSI Stanford Binet Verbal Performance Full Scale	C = 75 C = 30 Pb = 83 Pb = 36 Pb = 86 Pb = 84 C = 88 C = 87 C = 85	$p = 0.05$ N.S. N.S. N.S. N.S. N.S. N.S.	54
Athens, Greece	Mentally retarded With unknown etiology = 60 With known etiology = 30 Normals = 30	$\bar{x} = 8.4$ Range: 2-15 $\bar{x} = 8.5$ Range: 2-15 $\bar{x} = 8.4$ Range: 2-15	$\bar{x} = 30.1$ $\bar{x} = 20.9$ $\bar{x} = 20.8$	—	Comparisons of blood lead levels among institutional and normal control vs. MRs with unknown etiology	$p < .001$ (type of statistical test not reported)	70a

- * Mean test scores obtained for control children are indicated by C = $\bar{x}$; mean scores for respective lead-exposed groups are indicated by Pb = $\bar{x}$ (except for Rummo¹¹ study where C = control, S = short term lead exposed subjects, L = long term lead exposed group, and P = postencephalopathy lead group).
- * N.S. = nonsignificant, i.e., $p > 0.05$. Note exception of $p < 0.05$. Note exception of $p < 0.10$ listed for spatial ability results in Koiook et al.¹² study.
- * PbB data not necessarily obtained from same (or all) subjects providing behavioral data.
- * Or 30 $\mu\text{g}/\text{dl}$ or above with positive radiologic findings. The latter suggest earlier exposure in excess of 50–60 $\mu\text{g}/\text{dl}$.
- * Urinary coproporphyrin levels were not elated.
- * Assays for lead in teeth showed the Pb-exposed group to be approximately twice as high as controls (202 $\mu\text{g}/\text{g}$ vs. 112 $\mu\text{g}/\text{g}$, respectively).
- * Used for children over 5 years of age.
- * Pb in hair.
- * $\mu\text{g Pb}/\text{g ash}$.
- * Average of maximum PbB obtained during repeated testing of each child.

DDST failed to reach significance. When the scores of two groups were combined, it was found that the resultant group differed significantly from the DDST standardization group in the fine motor and language sectors. Finally, when the experimental and control subjects were grouped by environmental rating, it was found that the group with the poorest rating differed significantly from the one with the best rating in the fine motor and language areas on the DDST. The author concluded from this study that environment, and not lead toxicity, caused the developmental delays seen in these children.

This study has several flaws which damage its credibility. One primary problem is that no information appears to be available regarding the exposure histories of the subjects predating the time of the study. Thus, there is no way of knowing the degree to which the single blood lead taken at the time of the study is representative of the entire exposure history of the subject. Without this information one cannot be certain that the exposed and the control groups differed to any appreciable extent in their exposure to lead. Indeed, the possibility exists that in the long run there was considerable overlap in the exposure histories of the two groups. If so, there would be no reason to expect the groups to perform differently on the DDST. Compounding this problem, the mean blood lead for controls is somewhat high by present Center for Disease Control (CDC) Guidelines.⁴⁵ This further suggests that many of the controls had moderate levels of lead exposure and thus were similar in exposure history to some subjects in the "exposed" group.

Another major flaw in the study concerns the use of the DDST as the primary measure of development. The DDST is a screening instrument. As such, it is meant to screen large samples of children in order to find those with potential developmental disabilities. Children are scored pass or fail according to the number of items they attain at their own age level in each sector. This test was not meant to be quantified. Therein lies one major problem in this study. The author has assumed that one item per subject in each sector was representative of the developmental level of the child in that sector of behavior, e.g., gross motor development. The DDST was not meant to sample each sector broadly at each age level. Using a single score as representative of the child's ability probably does not give a true picture of the child's age-related skills in each area that was assessed. Thus, the behavioral data in this study may not have a high construct validity.

Other procedural errors of a lesser nature also compromised this study. For one thing, the rating of birth records and maternal interview information is a questionable procedure given the known lack of reliability and validity surrounding the way such data are or are not reported in records or in interviews.^{46,47} Thus, one would have to question the validity of the findings between the groups that were attributed to home environment. Likewise, 87% of the lead-exposed subjects had been chelated, thus possibly confounding exposure with treatment effects. Finally, statistical procedures were either incorrectly applied, e.g., the t-test was used with nominal data, or the procedures were not specified.

(2.) Kotok et al.⁴⁸

Subjects in this study were 67 children receiving medical care at three health centers in Rochester, N.Y. The control group was comprised of 36 subjects with a history of pica and blood leads below 40 $\mu\text{g}/\text{dL}$ (31 of the children had blood leads below 30 $\mu\text{g}/\text{dL}$). The study group was comprised of 31 subjects with blood leads ranging from 61 to 200 $\mu\text{g}/\text{dL}$ at their peak. All of the subjects in this group, except one, were asymptomatic at the time peak blood leads were recorded. In this group, 14 subjects were treated for lead poisoning with some form of chelation therapy. The two groups were matched on age, sex ratio, and past medical history. Subjects with medical histories

indicating CNS dysfunctioning were excluded from the study. The mean ages of the control and test groups were 42.6 and 43.4 months, respectively. The mean blood leads for the control and lead groups were 28.3 and 76.9 $\mu\text{g}/\text{dl}$, respectively. Subjects were given a test battery designed to test a broader range of mental ages than is ordinarily the case on psychometric tests. The dimensions included on this multidimensional test protocol included social maturity (the Vineland Social Maturity Scale), spatial relationships (Bayley blue board, Hiskey blocks, WPPSI block design), spoken vocabulary (Bayley vocabulary, Binet picture vocabulary, WPPSI vocabulary), information-comprehension (Binet objects, Binet parts of body, WPPSI comprehension), visual attention (Bayley pegboard, Hiskey beads, Knox cubes), and auditory memory (Illinois Test of Psycholinguistic Ability or ITPA). IQ equivalent (mental age divided by chronological age $\times 100$) was the primary dependent measure obtained for most of these measures. Additionally, specific memory and attentional factors were compared for each subject against the overall optimal level of functioning for the subject as determined by parental report, a measure of social maturity, and general intelligence factors. In this case, a deficit in these areas was defined as a score falling 15% or more below the subject's optimal level of functioning. All subjects were tested without the examiner having information regarding their previous blood-lead determinations. The results showed that the two groups differed on none of the above measures. Although, the range of scores was wide for each group, the authors suggest that this study, which controlled for pica, indicates that no difference was detected between the exposed and nonexposed subjects. However, they caution against interpreting this finding as indicating the absence of neurologic damage as a function of lead exposure since later longitudinal examination of these subjects might reveal such differences.

The credibility of the seemingly negative results rests primarily on the adequacy of the separation of the two groups in terms of lead exposure and in the adequacy of the behavioral measures used to test for differences. On both counts, this study appears weak. It appears that the authors did not closely monitor the lead exposure history of subjects and, thus, insure a reliable separation of exposure-over-time between groups. While the information presented to the reader is somewhat vague, it appears that just a few indices were used to determine exposure histories. As will be pointed out numerous times in this review, such a procedure is not acceptable for adequate documentation of lead exposure histories. Furthermore, no information is given as to when the blood lead determinations were made with respect to the age of the child. Hence, the reader has no idea if they were recent determinations, if they were made at various ages for different subjects, or if they were made at a time when these subjects might have been expected to be especially vulnerable to elevated lead exposure. This lack of information makes it very difficult to interpret the data. Mention should also be made of the fact 15 of the controls had blood leads between 30 and 40 $\mu\text{g}/\text{dl}$, a range which is considered unsafe by the 1978 CDC guidelines.⁴⁵ Even though the authors indicated that many of these subjects lived in relatively lead-free homes or resided in neighborhoods which had a low incidence of lead poisoning, the fact still remains that such a level of exposure, if prolonged, could have affected 40% of the control subjects in the same way as the test group. This would tend to minimize any difference between groups that might have occurred as a function of lead exposure. Finally, the whole issue surrounding how well these authors controlled for exposure history is complicated by the high range of blood leads reported for the test group subjects. The mean lead, plus the range reported, would indicate that many of these subjects fell far above 60 $\mu\text{g}/\text{dl}$, the boundary considered by most to be the upper limit of so-called asymptomatic lead poisoning.

The behavioral measures used in this study essentially represent a conglomeration of items taken from a variety of tests. When this is done, it is important to know

whether the particular combination chosen has been standardized in such a way as to have adequate age norms, reliability, and validity. None of this kind of documentation is provided in the report, although references are given. Given this lack of information, one has to question whether the tests were sufficiently standardized to permit the use of IQ equivalents as valid dependent measures. Likewise, doubts must be raised as to whether these tests measured the skill areas indicated by the authors. Without some definition of what these skills are, this is a difficult judgement to make. The reviewer's judgment is that the tests used to tap each of these skill areas may not have been pure enough or comprehensive enough. Finally, the dependent variables that were used to test memory and attention are sketchy. Not enough information was given as to how the subject's optimal functioning was measured using parental estimates and general intelligence. Thus, the measurement package employed in this study appears to be very weak in terms of standardization, validity, and the suitability of its quantitative scores. These factors, plus the aforementioned problems with exposure history documentation, seriously strain the credibility of the study.

(3.) Perino and Ernhart⁴⁸

In this study the authors tried to relate lead exposure to cognitive performance. The McSCA was administered to 81 preschool children whose blood levels of lead were assessed 2 weeks prior to the testing. Those children with blood-lead levels between 10 and 39 $\mu\text{g}/\text{dl}$ served as control subjects; those with levels between 40 and 70 $\mu\text{g}/\text{dl}$ were in the moderate exposure group. The groups were matched on age, sex, social economic status (SES), maternal intelligence (mothers were administered the Quick Intelligence Test), and birth weight. The controls were found to be significantly better than the exposed group on the GCI (90.14 vs. 79.83), the verbal (43.58 vs. 39.17), and the perceptual-performance (43.60 vs. 37.17) scales of the McSCA. These differences remained even after the effects of age, maternal IQ, and birth weight were accounted for in the variance. Furthermore, the correlation between the intelligence of the nonexposed children and their mothers was at the expected level ($r = 0.52$), whereas it was absent for the exposed children and their mothers ($r = 0.10$). The authors felt that this finding indicated that moderate lead exposure suppressed the usual relationship between the mother's and the child's IQ. When correlations were done between lead level and demographic variables such as socioeconomic status or the number of siblings, a significant negative correlation was found between lead level and parental education.

This is one of the better studies in the literature both in terms of maintaining a clearcut separation between the exposed and nonexposed subjects at the time of the study and in terms of using multivariate statistical procedures to test for the effects of lead over and above other significant and naturally co-occurring variables like socioeconomic status, birth weight, age, etc. The differences found on the McSCA are also quite large relative to statistically significant findings in other studies. More importantly, they are large enough to be of practical significance. However, there were flaws that occurred in the study which make it difficult to interpret the findings in the same manner as the authors. The subjects' exposure histories are inadequately documented with respect to level, timing, and duration of exposure. Without adequate experimental and statistical control over the lead exposure variable, there is doubt as to whether the statistical association between lead and test performance reflects effects of lead or the effects of some other variable. There is a suggestion in the data that the latter might have been the case. This suggestion comes from the significant negative correlation between lead level and parental educational level. This means that the more educated parents had children who were minimally exposed to lead. It is possible that these same parents were also more concerned about the health and the intellectual stimulation of

their children than were the less educated parents. Most importantly, however, is the possibility that the more educated parents gave their children more opportunity to learn and practice skills highly similar to those tapped on the McSCA. This fact, rather than lead exposure, could have accounted for the degree of difference found between the controls and lead-exposed children in this study.

(4.) Pueschel et al.⁴⁰

In this study, 705 children between the ages of 6 and 72 months living in Roxbury, Mass. were screened for lead exposure. Hair lead was used as an index of exposure. The mean hair lead in this sample of children was 118 $\mu\text{g}/\text{gm}$. This was in contrast to a city-wide average in Boston of 27 $\mu\text{g}/\text{gm}$. Blood leads were assayed on all of the children in the original sample who had hair leads equal to or greater than 100 $\mu\text{g}/\text{gm}$. The mean for this group was 37 $\mu\text{g}/\text{dl}$. Those children with blood leads above 40 $\mu\text{g}/\text{dl}$ were treated by chelation therapy and attempts were made to remove the source of lead exposure from their living environments. A small sample of children ($n = 58$) with high lead burdens were given an extensive evaluation which included histories gathered from a maternal interview, a neurological examination, and a psychological examination. The interview with the subjects' mothers indicated that a large but unspecified number of these children had pica. The neurological examination revealed that more of the lead-exposed children than the controls showed evidence of increased irritability. In addition, 15 out of the 56 children examined showed evidence of clumsiness and fine motor problems; only 5 out of the 48 controls had the same problems. This difference was statistically significant.

On the psychological tests, the lead-exposed subjects had a mean IQ score on the Binet or the Cattell (an infant intelligence test) of 86; no equivalent data were given for the controls. Data from the Sequin Formboard, the Berry VMI, and the behavior ratings (unspecified) "showed equivalent results" to those from the intelligence tests. A follow-up study of 42 of the lead-exposed subjects 18 months later indicated that there was improvement on the intelligence tests and on the Sequin Formboard, although no data were provided in either case. No change was noted in the scores on the VMI. Behavior problems and school failure were seen in some of these subjects at this time. Additionally, ratings of their behavior showed higher activity levels. Laboratory data revealed that the children, as a group, had a mean blood-lead level of 35 $\mu\text{g}/\text{dl}$ and continued to have elevated hair leads (mean of 92 mg/gm). The authors concluded that the screening for elevated hair lead was valuable in picking up children with significant exposure to lead, although it might not be sensitive to recent ingestion. They felt that they had found an "insidious" form of plumbism since 32% of their subjects showed neurological and psychological sequelae.

This study presents a number of major problems of a procedural nature which make its validity very doubtful. First there are the sampling procedures. The authors give no specification as to how they arrived at the final study sample and there is no way of knowing how representative that sample was of the population of children who had asymptomatic levels of exposure. A further difficulty stems from the fact that all of the sample subjects underwent some form of chelation therapy. This means that the testing data are confounded with treatment effects. Thus, it is difficult to compare these results with those from other studies where treatment was not a factor.

A third problem resides in the failure to define the criteria used to make neurological and psychological evaluations. The reader is not told, for example, how it was determined that a child was irritable or clumsy. Nor is any specific information given about the nature of the behavior ratings that were used in this study. Omitting information of this kind makes it difficult for the reader to understand the true nature of these deficits, and it makes it impossible for another investigator to replicate the study.

Another problem arises from the way in which the data were reported. For example, on the neurological examination comparisons were made with a control group whose nature was unspecified. In other instances no such comparisons were made. The latter is especially evident in the reporting of the intelligence test scores for only the experimental group. We have no idea whether the mean IQ of 86 for the exposed group is high or low in comparison to a control group. This is especially confusing since such an IQ score of 86 would not be unusual, given the bias of most IQ tests, for a population of inner city black children without health problems. Thus, without appropriate control data it is hard to interpret the intelligence test data as they were reported in this article. Equally troublesome is the fact that in many instances data on particular measures were not reported at all. The reader has to trust the judgment of the authors as to the nature of the reported differences and their meaning. Statistical tests are rarely reported even though the reader is told, for example, that the lead-exposed subjects improved on the testing done 18 months after the original testing.

Again, there was only one measure of exposure which was presumed to be indicative of the total lead exposure history of the subjects. Problems with this kind of assumption have already been detailed in a previous critique (see Kotok⁴⁴). The present study is further compounded by the fact that a wide age range of children were screened and there is no way of knowing if timing of exposure, let alone the dose and duration factors, were or were not roughly equivalent for all subjects. It is indeed possible that the timing of exposure for some of the subjects occurred at ages when they might have far been less vulnerable to the effects of such exposure. This ultimately has the effect of making the test group more similar to the control group in lead exposure, which might in turn mean that less marked differences attributable to lead would be found. The fact that differences were obtained might indicate that the lead effect in this study was quite strong and the differences between the groups would have been more striking if this problem had not occurred. However, it is questionable that a lead effect was clearly demonstrated in this experiment mainly because of the aforementioned failure to provide appropriate group comparisons on crucial data and because of the lack of reported statistical analyses on much of the data.

(5.) Needleman et al.¹¹⁸

In this study the authors sampled tooth-lead concentrations in 3329 children attending the first and second grades in Chelsea and Somerville, Mass. during the years 1975 to 1978. Children with dentine-lead concentrations in the highest 10% of the distribution (≥ 24 ppm) and in the lowest 10% of the distribution (≤ 6 ppm) comprised the high- and low-lead groups, respectively. Children were excluded from the study if they came from bilingual homes, if they had poor health histories, or if the parents refused to allow them to participate in the study.

In order to get relevant demographic and social information about these children, the parents were asked to fill out a health and social history questionnaire, a 58-item questionnaire on their attitudes toward their children, and to take the Peabody Picture Vocabulary Test (PPVT). The 58 subjects in the high-lead group and the 100 subjects in the low-lead group were given a battery of tests to assess their neuropsychological status. This battery included measures of intelligence, concrete operations intelligence, academic achievement, auditory and language processing, visual-motor competence, attention, and motor coordination. In addition, the entire sample of children had their classroom behavior rated by their teachers on an 11-item, forced-choice (yes or no) rating scale (the teacher behavior rating scale). The parental questionnaire and maternal test data provided information on possible social variables, other than lead exposure, that might effect the subject's developmental status. Those variables on which the groups differed significantly were then used as covariates in the analysis of the test data.

The results of these analyses showed that the low-lead group performed significantly better than the high-lead group on overall I.Q. (106.6 vs. 102.1), verbal I.Q. (103.9 vs. 99.3), verbal subtests (information, vocabulary, digit span) of the WISC, the Sea-shore Rhythm Test, the Token Test, the Sentence Repetition Test, and on the last three-trial-blocks of the reaction time task. In addition, the groups differed in the expected direction with regards to the percentage of subjects in each group receiving negative ratings on each item of the teacher behavior rating scale. Finally, there were indications of a dose-response relationship for the entire sample in terms of the percentage of negative ratings on each item of the teacher behavior rating scale. The authors concluded that their results suggest that moderate lead exposure affects verbal and auditory processing ability as well as attentional abilities.

In many ways this is one of the better designed studies in the literature. The authors tested a broad sample of children, utilized a measure of lead exposure that presumably indexes both duration and level of exposure, tried to control for confounding social variables, used a comprehensive battery of behavioral measures, and utilized statistical techniques that could test for a lead effect over and above those caused by other variables. The finding of processing and attention deficits is somewhat unique to this literature and may offer a promising lead as to nature of the lead effect. Unfortunately, there were some problems with this study which served to weaken its value in terms of the information it provided on the question of lead effects on children's development.

A major question in this study arises from the interpretation of the behavioral findings. Reported behavioral differences between the groups were typically quite small. This raises the question as to whether results of such a small magnitude have any practical meaning in predicting the everyday performance of the subjects in these two groups. The four-point difference in IQ found between the groups on the WISC is a case in point. It seems unlikely that such differences alone would indicate that the children in these two groups reliably differed in their academic performance. However, differences of this magnitude might have meant that more of the exposed children were retarded (i.e., had IQ scores below 70) or were significantly deficient in their verbal skills. This hypothesis was not statistically tested in the study. It could have been tested by looking for differences in the distribution of these scores or by testing to see if more of the exposed subjects were mentally retarded (i.e., had IQ scores below 70). Unfortunately, only group mean IQs devoid of estimates of variance were reported.

The interpretation of the teachers' ratings of classroom behavior also appears to be tenuous. First, no information was given on this scale's properties in terms of its reliability and validity. Hence, the reader has no idea how repeatable and accurate these ratings were in terms of differentiating the classroom behavior of the children. Secondly, the investigators appeared to treat each item on this scale as a measure of a separate behavioral dimension. It is doubtful that a single forced-choice item provides a comprehensive, precise, and reliable measure of a behavioral dimension. Finally, both groups, in spite of the differences obtained between them, appeared to have evidenced a very low frequency of negative behavior on these ratings. All this weakens the overall credibility of the data provided by these ratings. This, in turn, weakens the authors' claim that there was a dose-response relationship between lead level and percentage of negative ratings on each item, a claim that in any case was never put to a statistical test.

The documentation of the lead exposure variable, while adequate, still leaves many questions unanswered. It appears that the investigators did a good job of separating the two groups in terms of prolonged lead exposure. However, dentine-lead concentration, as used in this study, still gives no information as to when the experimental subjects were exposed to lead or if they were chronically exposed at doses above a safe

level. Dentine-lead concentrations must be thoroughly validated with respect to historical blood lead levels before these data can be of use to regulatory agencies or the medical profession.

b. Lead Screening Prior to Behavioral Evaluation

(1.) Rummo¹¹

In this study, lead-exposed subjects were divided into the following groups: (1) a lead encephalopathy group characterized by two blood leads (obtained 6 months apart) above 40 mg/100 dL and one or more symptoms (like lethargy, convulsions, or ataxia) that are usually indicative of lead encephalopathy; (2) a long-term exposure group characterized by two blood leads above 40 and accentuated epiphyseal lead lines; and (3) a short-term exposure group characterized by one blood lead above 40. These subjects were matched on a pair-by-pair basis with 45 controls in terms of age, sex, and race. The subjects were given both a neurological and a psychological examination. The former consisted of measures of balance, tandem gait, finger-wrist tapping, auditory reaction time, and visual reaction time. The psychological evaluation consisted of an administration of the McSCA, a matching-to-sample task wherein the child had to match alternative models to each VMI figure, a tracing task in which each subject had to trace over each VMI figure with a felt tipped pen, and the WWP Activity Scale.

On the neurological exam, the lead encephalopathy group was statistically different from the controls on the tandem gait, the balance, the wrist tapping, and the reaction time measures. None of the other lead-exposed groups differed from controls on this examination. Results from the psychological evaluation generally showed that only the lead encephalopathy group differed significantly from controls on any measure. This held for the GCI (75.7 for the lead encephalopathy group vs. 93.3 for the controls) and on the scale scores (e.g., memory, perceptual-performance, etc.) from the McSCA. These differences were found on a univariate analysis of variance, but not on the multivariate analysis of variance where the effects of age, sex, birth history, and other variables on this measure were taken into account in the data analysis. This same group differed significantly from controls in activity level as measured on the WWP. No differences were seen between groups on either the matching-to-sample or the tracing task, although the author does report a difference between the lead encephalopathy group and the control group when the measure used was the number of children with less than 50% correct on these tasks. The author concludes by stating that the findings replicate others reporting the deficiencies of lead-poisoned subjects except for the finding of no differences in visual-motor functioning and the frequency of behavior problems. She further concludes that there does not appear to be any behavioral deficits in children with asymptomatic levels of lead exposure.

In many ways, this is one of the better studies in the literature. The composition of the groups is such that there is, ostensibly, very little overlap in the blood-lead distribution of the groups. The McSCA, as a single vehicle to measure the effects of lead, is probably good in the sense that it measures skill areas like perceptual-motor ability that could be damaged by this kind of insult. Finally, the use of multivariate statistical procedures put the investigator in the position of assessing the effects of lead over and above the effects attributable to other variables.

Yet, this study is plagued by some of the same problems that have marred the studies previously reviewed. There is very little information regarding the true exposure history of the subjects in this study. We have no way of knowing whether the one index of exposure represents an exposure history that has prevailed long enough to really affect the child. Certainly the blood-lead levels in the two asymptomatic groups at the time of screening were high (a mean of $61 \pm 7 \mu\text{g}/100 \text{ mL}$ for the short exposure group and $68 \pm 13 \mu\text{g}/100 \text{ mL}$ for the long-term exposure group), however, one cannot be sure

that these values were not the result of a recent short-term peak exposure. Information regarding when the subjects were screened is also lacking. We have no information indicating the age interval during which the subjects were exposed to lead. These factors could have made the asymptomatic groups more like the control group resulting in the lack of differences found in this study.

(2.) Albert et al.²²

The subjects in this study were obtained from 371 names on the lead registry of New York, N.Y., were siblings of children on the lead registry, or were children from high-risk areas that had been assayed for lead exposure using tooth lead as an index of exposure. Of the subjects used in this study, 40% were available from the registry. The authors state that this available sample was equivalent, in terms of demographic characteristics, to those cases from the registry that could not be located. These subjects were then, on the basis of blood- and tooth-lead data, placed in one of the following groups: (1) encephalopathy, treated ($n = 6$); (2) no encephalopathy, treated ($n = 154$); (3) high blood leads (65 children with blood leads above $60 \mu\text{g/dl}$); (4) low blood leads, high tooth leads (24 subjects with blood leads $\leq 60 \mu\text{g/dl}$ and tooth leads $> 58 \text{ mg Pb/g ash}$); and (5) low blood lead, low tooth lead (89 children with blood leads below $60 \mu\text{g/dl}$ and with a median tooth lead of 12 mg Pb/g ash). The lead screening was done on these subjects at a mean age of $2\frac{1}{2}$ years. The followup evaluation testing was conducted at a mean age of 6.7 years with a range of 3 to 11 years. For all subjects, the following data was collected: health status, social status (via maternal interview), and school records (including hearing and vision test data). A subsample of this population ($n = 149$), all above 7 years of age, was brought in for a psychological evaluation. This evaluation consisted of the WISC, Bender Gestalt, DAP, and the Purdue Pegboard. In addition, school records were checked in terms of grades, grades failed, teachers' ratings of behavior, test scores, and referrals for psychological services. Group 5 was designated as the control group, and as such, comparisons were made between it and the other groups. Results of the psychological testing showed that Group 1 (mean IQ = 77.0) and Group 3 (mean IQ = 92.4) differed significantly from Group 5 (mean IQ = 98.9) on the WISC. The same trend held for the reported results on the Bender and the Purdue Pegboard. Only Group 1 differed from the controls on the DAP. When a clinical psychologist used the test data to make a composite rating (on a five-point rating scale) of organic impairment on each subject (without knowledge of lead exposure), Group 1 had a significantly higher rating for organicity than did Group 5. In terms of mental disability, Group 1 had a high rate of mental retardation, but nothing else. Group 3, on the other hand, appeared to be at significantly high risk for seizure disorders, behavior problems, and mental retardation. Both Groups 1 and 3, in comparison to the controls, showed significantly higher frequencies of school problems, including failing a grade, special class placement, referrals for psychological services, and disorders of attention and concentration. Finally, the authors indicated that probably 43% of the subjects in Group 3 were symptomatic for lead poisoning at one point in their lives. When the symptomatic and asymptomatic subjects in this group were compared, the preponderance of low psychometric test scores, school problems, and mental disorders were found in the symptomatic group. The asymptomatic subjects in Group 3 differed from the controls only in the number of children having mental problems, having difficulties with attention and concentration, and having been referred for psychological services. The authors conclude that lead has deleterious effects on behavior, but probably not at asymptomatic levels.

A number of procedural errors appear in this study which cast some doubt on the validity of the findings and the conclusions drawn from these findings. To begin with, the sampling procedure is confusing. It would appear that the authors relied on a

"handy" sample, i.e., one that was readily available for the purposes of this study. Despite their assurances that the available subjects were similar to the population as a whole, it is possible that these subjects differed from the unavailable subjects in ways that would both increase the likelihood of lead exposure and decrease their functioning on a number of behavioral measures, i.e., being raised in a home where there was little concern for the child. Lack of adequate control for this possibility makes it hard to interpret the findings as solely attributable to lead exposure. The sampling procedure, especially with respect to whether or not tooth lead was a main criterion for grouping subjects, is also vague and confusing. Finally, and most importantly, the value of Group 3 was badly compromised by being a mixture of symptomatic and asymptomatic children. The authors, cognizant of this mixture, reported the differences in behavior between the subjects within this group. However, little could be inferred about the effects of *asymptomatic* lead exposure from comparisons between Group 3 vs. Group 5.

Exposure history, or lack thereof, represents another major problem for this study. We have one index of the entire exposure history of the subject with all of the attendant problems that have been previously noted. Again, there is some possibility that the indices of exposure were obtained at different ages for different subjects, thus leaving the question of the timing of the exposure unresolved. The authors did, to their credit, use tooth lead as an index of long-term exposure. However, there were no behavioral differences reported between the high- (Group 4) and the low-tooth-lead (Group 5) children. If anything, an examination of the data suggested that the group with a presumed long-term lead exposure (high tooth lead) performed somewhat better, though not in a statistical sense, than the group with a short lead exposure history. Finally, it appears likely that there was some overlap in the blood leads of the asymptomatic and control groups. Groups 4 and 5 had median blood leads of 40 $\mu\text{g}/\text{dL}$, while Group 3 had a median blood lead of 70 $\mu\text{g}/\text{dL}$. However, one wonders if the truly asymptomatic subjects of this latter group might have had blood leads closer to those for Groups 4 and 5, thereby working against the detection of significant differences between asymptomatic and control subjects.

The dependent measures used in this study were also suspect. Grades, teacher ratings, and other school data, were used even though they are known to be subjective and unreliable. Reliance on such data as an index of the behavior and academic performance of the subjects is not as adequate as the use of objective measures that tap these same facets of behavior. The use of IQ as a behavioral measure may be too global to pick up differences in specific skill areas that might have been affected by lead exposure. Moreover, the statistically significant IQ differences that are reported between Groups 3 and 5 are so small (6 points) as to be of little real significance. The use of other psychometric measures to tap perceptual and perceptual-motor skills is laudable, but the use of only one test in each behavioral domain may not have been comprehensive enough to insure the detection of significant deficits.

Finally, one must make some mention of the statistical procedures used in this study. Specifically, numerous "t"-tests were performed on the data. The authors seem to disregard the dictum that one can inflate the probabilities of finding significant "t" values by chance alone by increasing the number of such tests that are performed on the data. An analysis of variance, even though some assumptions for this test might have been violated, would have been more appropriate prior to the use of "t"-tests.

(3.) Baloh et al.²²

In this study, asymptomatic lead-exposed children ($n = 27$) were identified on the basis of having at least two screening blood leads greater than 50 $\mu\text{g}/\text{dL}$ and being

older than 3½. The latter restriction was for the purpose of getting reliable psychometric test scores. A like number of control subjects who had blood leads of $< 30 \mu\text{g}/\text{dl}$ 9 months previous to the testing were given the same tests. Subjects from both groups were matched on age, sex, SES, and race. All subjects were given a physical examination which included "quantitative" neurological tests such as finger-wrist tapping, length of time standing on each foot, two-place alternate tapping with each hand, hole steadiness with each hand, and auditory and visual reaction time. The subject's emotional behavior during this examination was also recorded. Additionally, subjects underwent extensive psychological testing. They were given portions of the WPSI or WISC depending on their age. The psychological test battery assessed the child's skills in the following areas: motor (the leg and arm coordination subtests from the McSCA and the Wallin Pegboards), perceptual-motor (the animal house and geometric designs subtests from WPSI, the mazes subtest from either the WPSI or the WISC, the block designs subtests from the WISC and the block building and the tapping sequence subtests from the McSCA), verbal-cognitive (the information and vocabulary subtests from either the WPSI or the WISC), memory (the tapping sequence, pictorial memory, and digits forward and backward subtests from the McSCA), and quantitative (the arithmetic subtest from either the WPSI or the WISC).

No statistically significant differences were found on the IQ scores (89.2 for the lead-exposed group, 89.8 for the controls) or on any of the other psychological measures. The same held for the findings from the physical examination. The authors state that there were some trends in the data, not statistically significant, indicating that the lead-exposed subjects might have been worse than the controls on measures of fine- and perceptual-motor skills. They conclude that this study generally showed no evidence for neuropsychological deficits in children with so-called asymptomatic lead exposure.

One of the most noteworthy aspects of this study is the authors' attempt at providing a neuropsychological examination on each subject. In this sense, giving each subject several tests in a given skill area is an improvement over the more traditional reliance, seen in most studies in this area, on the global IQ score and a single measure of motor or perceptual motor skills. However the investigators might have obtained the same information, with more precise age norms, by simply administering the McSCA to their subjects. In some ways this would have made more sense since the GCI (an IQ equivalent) would have been based on more comprehensive testing than were the IQ scores reported in the study. Indeed, no information was given as to how these IQ scores were obtained.

A major problem with this study is the fact that there could have been considerable overlap in the exposure histories of the two groups. The fault here appears to lie with the fact that the lead-exposed subjects were selected on the basis of two screening measures apparently obtained some time before the evaluations. The controls were selected in a similar fashion, but only 9 months before the behavioral evaluations. The groups, as constituted, appeared to be different at the time of testing since the lead-exposed group had a mean blood lead of $44.2 \mu\text{g}/\text{dl}$ and the control group a mean of $24.6 \mu\text{g}/\text{dl}$. However, this may be deceiving. For example, it appears that the blood leads of the experimental subjects decreased from the time they were initially screened to the time they were tested. In this group, nine of the subjects (33%) had blood leads that had decreased by at least $20 \mu\text{g}/\text{dl}$ by the time of testing. Furthermore, 14 of these subjects had blood leads that were by then below $50 \mu\text{g}/\text{dl}$ (the classification cutoff), and nine had blood leads below $40 \mu\text{g}/\text{dl}$ (one as low as $13 \mu\text{g}/\text{dl}$). In addition, six of the controls had, at the time of testing, shown increases in their blood lead to the point that they fell between 30 and $40 \mu\text{g}/\text{dl}$. Apparently there was considerable variability in the exposure history of these individuals which would serve to lessen the chances of detecting significant group differences.

(4.) Sachs et al.⁴⁴

The effects of lead exposure were studied by comparing 47 lead-exposed and nonexposed children on a battery of psychological tests. Experimental subjects were selected on the basis of having had blood leads above 79 $\mu\text{g}/\text{dl}$ on a lead screen done 2 to 8 years prior to the study as well as on other indices (e.g., radiographic) indicating exposure. These subjects were between 14 and 72 months of age at the time they were screened. Their blood leads ranged from 50 to 365 $\mu\text{g}/\text{dl}$. Of these children, 18 had at one time been symptomatic for lead poisoning. All exposed subjects had chelation therapy. Siblings close in age to the affected child were used as control subjects. The latter subjects had blood leads below 40 $\mu\text{g}/\text{dl}$ at the time they were screened. Siblings were used as control subjects because it was felt that this controlled for genetic, social, and cultural influences on test scores.

All children were given a neurological and a psychological examination. The latter consisted of a WPPSI or WISC, depending on the age of the child, the VMI, the Ravens Progressive Matrices, and the DAP. The parents of these subjects were questioned regarding whether or not their children exhibited troublesome behavior at home, school, or at play. The data were analyzed using a Wilcoxon Signed Ranks Test for Matched Pairs.

The results from the neurological evaluation showed no differences between these two groups of children. The psychological test data also failed to differentiate between these two groups of children. However, the lead-exposed children had lower arithmetic subtest scores on either the WPPSI or WISC. The authors also found no differences between the groups in the frequencies with which parents reported a child displaying negative behavior.

Disparities between these two groups did occur in the sense that the lead-exposed subjects generally outperformed their sibling control on two of the verbal subtests and all of the performance subtests. However, these differences were not statistically significant. The authors also found a correlation of 0.42 between the IQ scores of the matched pairs. This, they stated, was close to the expected relation siblings should show on this measure if nothing is affecting the intelligence of one member of the pair. Finally, the authors found no differences on psychological test scores when index subjects and their control siblings were grouped by lead level, when the 18 symptomatic children were compared to their sibling controls, or when pairs were examined where the index child had a blood lead $\leq 200 \text{ mg}/100 \text{ dl}$. The authors concluded that genetic factors had a stronger influence than lead exposure on this set of test data. They also suggested that early treatment for lead exposure decreased the likelihood of finding behavioral sequelae.

A major problem with this study was the procedure used to control for confounding variables, i.e., a sibling control group. It is clear from the data presented by the investigators that many of the siblings in the control group exhibited a significant degree of mental retardation. The authors report that all of the children in two of the six families with an index child with a blood lead $\leq 200 \mu\text{g}/\text{dl}$ were moderately to severely retarded. Perusal of the data shows an additional control subject exhibiting mild retardation. Retardation in the control group would certainly operate to reduce differences that might exist between the groups due to lead exposure. The results would be more interpretable had the investigators included a control group of children who were known to be healthy and intellectually normal and from the same cultural background. They also had the option of collecting pertinent social, health, and demographic data on each subject in the study and using this information to parcel out the effects of variables, other than lead exposure, on test scores. The path the investigators chose to take, i.e., sibling controls, seriously weakens the credibility of the findings.

A second problem with this study is the lack of adequate documentation of the

exposure history variable. Only one blood lead (or radiographic or historical evidence of lead poisoning) was used to select subjects. This blood-lead determination was made 2 to 8 years before the study, and some of the children at that time were 6 years old. The authors assumed that this one measure of lead burden adequately characterized the entire exposure history of a subject. However, the information given in the body of the report tells us nothing about critical exposure parameters like the timing, the dose level, or the duration of the exposure. Nor can we take much stock in the authors' contention that the controls were nonexposed just because they moved to safe housing following chelation of their sibling. Other studies have indicated that such a change in housing does not automatically rule out the possibility of elevated exposure.^{14a} While the separation between the exposed and control group seems real enough, the lack of information regarding the timing, duration, and doses of such exposures makes it difficult to know for sure that the lead-group subjects were chronically exposed to dose levels in the so-called asymptomatic range.

A final concern with this study pertains to the sampling procedures used to obtain study subjects. The authors provide no demographic or social data regarding these families. Therefore, it is difficult to ascertain if these findings are generalizable to children who are typically exposed.

This study fails to support the authors' conclusions that chelation therapy negates later behavioral sequelae, nor do the findings of this study seriously question the possibility of neurobehavioral sequelae resulting from such exposure.

c. Subjects Identified by Presumed Source of Exposure

(1.) *de la Burde and Choate¹⁵*

All children who participated in this study were part of the Collaborative Study on Cerebral Palsy, Mental Retardation, and Other Sensory Disorders of Infancy and Childhood. This particular cohort of 3400 children was being followed at the Medical College of Virginia in Richmond. Lead-exposed subjects were selected on the basis of guidelines in part prescribed by the Collaborative Study. Initially, children were determined as having possible lead exposure only if their mothers reported that they engaged in pica. Experimental subjects were then selected from this subsample of the cohort if they met the following criterion: lived in delapidated housing, had positive urinary coproporphyrin levels and blood leads greater than 40 $\mu\text{g}/\text{dL}$, or had blood leads above 30 $\mu\text{g}/\text{dL}$ with additional radiographic evidence of lead exposure. In all, 70 such children were selected for study, although 3 were eventually excluded because signs of CNS anomalies were found in their infant examinations. The mean blood lead of this sample was 58 $\mu\text{g}/\text{dL}$ with a range of 40 to 100 $\mu\text{g}/\text{dL}$. Seventy control subjects were selected on the basis that they lived in recently built housing or housing that was in good repair and did not exhibit elevated urinary coproporphyrin levels. The two groups were matched on age, sex, maternal IQ, SES, number of siblings below 6 years of age, and housing density. All children were given a psychological evaluation when they were approximately 4 years of age. The psychological testing and subsequent coding of the data was done without knowledge of the subject's lead-exposure status. Intelligence was assessed using the Stanford-Binet. Fine-motor development was assessed by administering a form copying test, the Wallin Pegboard, a bead stringing task, and the Proteus mazes III and IV. Gross-motor development was assessed through the administration of a line-walking task, a ball-catching task, and the child's ability to hop. Concept formation was assessed by administering the Graham-Ernhart block sort test. Finally, a behavior profile was done on each child. This consisted of rating the child on ten five-point rating scales. The child's performance in each area was coded into a category depending on his or her test score. For the Binet, a child could be coded as being normal, borderline, or mentally defective, depending on his IQ score.

On the fine-motor tasks, the child was coded as being normal, suspect, or abnormal, depending on whether the subject passed all three of the tests, two of the tests, or only one of the tests. The same system was used for the gross-motor assessments except that the child's performance was scored as normal, suspect, or abnormal, depending on whether two, one, or none of the tasks were passed. Performance on the Graham-Ernhart sorting test and on the behavior profile was coded in the same manner, but no criterion for this coding was reported. The dependent variable was the number of subjects in each group who fell into the suspect and abnormal categories. The normal category was excluded from the analysis. Results, using a chi square, showed that the control subjects significantly outperformed the lead-exposed subjects on the measures of intelligence, fine-motor skills, and behavior. In terms of the latter, extreme negativity, distractibility, and constant need for attention, as a "triad", was found significantly more frequently (chi square analysis) in the lead-exposed than in the control subjects. An additional chi square analysis showed that the lead-exposed children, in comparison to the controls, had a significantly greater chance of having at least one behavioral deviation. The authors concluded from the results that asymptomatic lead exposure does have developmental sequelae.

The interpretation drawn by the investigators rests on the degree to which these groups differ as a function of lead exposure. Unfortunately, there are aspects of this study which leave serious doubts regarding this issue. The exposure history is not well documented in this study. Experimental subjects were selected on the basis of a history of pica and controls on the basis of residing either in new or rehabilitated housing (although no blood leads were obtained on these subjects to verify that they did not have elevated lead levels). There is reason to doubt the wisdom of this procedure. Later studies by de la Burde and Shapiro⁵⁴ indicate, for example, that a small sample of the control group had elevated blood leads (mean = 53 $\mu\text{g}/\text{dL}$). Furthermore, data from this latter study⁵⁶ indicated that many mothers later denied the once-reported history of pica in the experimental subjects. Just as importantly, this same study showed that a history of pica did not differentiate the blood and tooth leads of the experimental and the control subjects if the control subjects lived in older rehabilitated housing. Thus, there is some question as to whether these two groups, as selected, actually differed in degree of asymptomatic exposure. To this must be added the by now well-worn caveat that one index of lead exposure, at a single point in time, is not an adequate way of determining the lead history of a child in terms of critical parameters like the dosage, the duration, and the timing of the exposure. Thus, there are sufficient grounds for being suspicious about whether or not these two groups actually differed on the critical exposure variable.

One might well ask why these groups differed behaviorally. One strong possibility is that as initially constituted, the groups differed on a critical social variable, e.g., parental attitudes toward their children, that might have been responsible for the observed differences between them. This is based on a line of reasoning which suggests that parents who manage to get into newer housing or to live in housing which they themselves have repaired or which they have had repaired, may have different attitudes toward their children in comparison to families who remain in old, dilapidated housing. It is possible that the former set of parents are much more interested in their child's health, nutrition, emotional functioning, and intellectual development than are the latter families. If this were true, the differences found may well have been due to social variables and not lead exposure. This problem here speaks not only to errors made in the initial composition of the groups, but to failures in proper matching of experimental and control subjects in order to insure comparability on all variables except lead exposure. This is especially true on social variables. Demographic variables like socioeconomic status which are often used as matching variables are not a sensitive

and direct measure of family attitudes toward child care. These attitudes, rather than social class, probably exert a more potent influence on the child's development. Matching on direct measures of this variable would be more preferable than continuing to rely on matching on the basis of the less sensitive SES measure.

Finally, the statistical treatment of the test data casts some suspicion on the validity of the findings. First, there is no good rationale for taking quantitative test scores like IQs and turning them into frequency data, i.e., the number of children in the normal, suspect, and abnormal categories. There were additional problems with the coding and the statistical handling of the coded data. For example, nothing in the report indicates what denotes a passing or failing score on a given test. Without such information the data are hard to interpret and the study is next to impossible to replicate. Finally, data from subjects whose performance was classified as "normal" was excluded from analysis. Statistical analyses were applied only to the "tails" of the control and experimental group distributions. Such a procedure inflates the chances of getting a significant finding. Indeed, when the reviewer applied a chi-square analysis to all of the data and used a correction for discontinuity, the resulting chi squares turned out to be insignificant. Given these problems, one is left with the feeling that the differences found here may have been more apparent than real.

(2.) de la Burde and Choate¹⁷

This is a report of a follow-up study on the same subjects as reported on in the 1972 study. In this case, the subjects were given a neurological examination when they were 7 and again when they were 8 years of age. When they were 7 years old, they were also given an extensive psychological test battery. This battery included the WISC, the Bender-Gestalt, the Wide Range Achievement Test (WRAT), the DAP, the auditory-vocal association subtest from the ITPA, the tactile finger recognition test from the Reitan Indiana Neuropsychological Battery, and a behavior profile consisting of 15 five-point rating scales. Blind ratings of normal, suspect, or abnormal were made by the examiners according to protocols developed by the Collaborative Study. This was done for both the neurological examinations and for the performance on each test in the psychological test battery. Chi-square analyses were applied to this data. The results revealed that significantly more lead-exposed than control subjects performed in the suspect and abnormal categories on both neurological examinations. The same difference between the groups held on the psychological testing in terms of total IQ and for performance on the Bender, DAP, tactile finger recognition, and behavior profiles. Behavioral characteristics for the experimental subjects, as a group, included lack of confidence, fearfulness, and constant need for attention. School records for a proportion of subjects in each group showed that more experimental subjects had made poor progress, not because of low intellect, but because of being hyperactive, explosive, and impulsive. None of the control subjects exhibited this kind of behavior. Maternal interviews indicated that the lead-exposed children were more frequently engaged in delinquent behavior than the controls.

Nothing occurred in this follow-up study to repair the faults that seriously damaged its predecessor. If anything, we know even less about the experimental and control groups with respect to what happened to the subjects in the ensuing 3 to 4 years in terms of lead exposure, health problems, or social problems. No information is given about the nature of the neurological examination, so we have no way to interpret the data resulting from it. Likewise, the system of coding applied to each test score is even more vague and unspecified than that reported in the earlier study. Finally, there is every indication that the statistical procedures employed in this study were just as questionable as they were in the first study. School records and maternal interviews were apparently not subjected to statistical analyses. It is difficult to interpret these findings conclusively given all of these deficiencies.

(3.) Landrigan et al.²⁸

This is a study where airborne lead was presumably the source of exposure. In this case, all subjects lived within 6.6 km of a lead smelter plant. Exposed and nonexposed subjects were identified on the basis of a lead screening done in 1972. The control group was composed of children with blood leads below 40 $\mu\text{g}/\text{dl}$. The lead absorption group contained subjects with blood leads above 40 $\mu\text{g}/\text{dl}$. The mean blood lead for the controls, based on this screening, was 26.9 $\mu\text{g}/\text{dl}$ (range: 1 to 39 mg/dl). The mean for the exposed group was 48.3 $\mu\text{g}/\text{dl}$ (range: 40 to 68 mg/dl). The mean age for controls at the time of the testing was 7.8 years, while that for the experimental group was 8.3 years. All subjects were given a medical and neurological examination. The latter included measures of finger-wrist tapping, two-place alternative tapping, tandem walking, time standing on one foot, and auditory and visual reaction time. The psychological examination given at this time included short forms of either the WISC or the WPPSI, depending on the age of the child, and the Bender. Intelligence testing was done on a bilingual basis to accommodate children who spoke Spanish. In addition, mothers were interviewed regarding the child's health history and incidence of pica. The parents also rated the child on the WWP.

Results of the neurological examinations showed experimental subjects to be significantly slower on the finger-wrist tapping test. The only significant IQ test results showed that the experimentals were significantly poorer than the controls on the WISC performance IQ (96.44 vs. 103.29), the WPPSI performance IQ (90.67 vs. 100.27), and on the combined performance IQs (94.93 vs. 102.71). The authors concluded these findings suggested that subtle neuropsychological sequelae resulted from asymptomatic lead exposure. However, they pointed out that these differences may not have had any long-term developmental significance. Since the incidence of pica did not differentiate the groups, they felt that lead particulate matter in the air was responsible for the observed blood-lead values.

There are difficulties with this study posed by the way in which the exposure history was handled which make it likely that the lead exposure and control groups were more alike than the 1972 screening data would have indicated. For one thing, the use of one index of exposure, as indicated throughout this review, does not provide the investigator with the critical parameters regarding the subject's entire exposure history that are vital to interpreting the data. Furthermore, the screening was conducted when the subjects were well above the ages typically felt to be critical for lead exposure, leaving in doubt their early and potentially more critical lead exposure history. Data presented by the authors suggests that the screening leads were variable and that there was potentially considerable overlap in the degree of exposure for the two groups. When blood-lead levels for these children were obtained a year after the group assignments were made, the control subjects were relatively stable with only two children having blood leads above 40 (the mean for the group in 1973 was 26.9 $\mu\text{g}/\text{dl}$). On the other hand, the blood leads for subjects in the exposed group appeared to have declined significantly. In this case, 22 of the 46 subjects in the exposed group now had blood leads below 40 $\mu\text{g}/\text{dl}$ and the mean blood lead for the entire group had declined from 48.3 $\mu\text{g}/\text{dl}$ to 40.5 $\mu\text{g}/\text{dl}$. This creates some uncertainty about whether or not the groups had significantly different lead exposure histories. Thus, the investigators may have stacked the cards against themselves. The fact that significant differences were observed suggests either that the lead effect in this case was very strong or that another uncontrolled variable was responsible for the effect.

Another concern with this study was the reliance on global measures of intelligence. The findings produced suggest that lead absorption at moderate levels may have had psychomotor sequelae in the exposed subjects. Ideally, the testing should have exploited this possibility. In this study, as in others, too few tests were done to adequately sample psychomotor abilities as well as other significant behavioral domains.

(4.) McNeil, Ptasnik, and Croft⁴¹

The purpose of this study was to see if neuropsychological deficits could be found in a group of children who had undergone chronic exposure to asymptomatic levels of lead. All 138 subjects resided in "Smeltertown", an area outside of El Paso that is isolated by the Rio Grande River and a lead smelter. This is the same area from which Landrigan et al.⁵⁸ drew subjects for their study. Of these subjects, 101 were known to have blood lead levels above 40 $\mu\text{g}/\text{dl}$. These formed the experimental group. Controls were children who lived in El Paso at a distance of either 3.2 or 4.8 km from the smelter. Each control subject was pair-matched to a test subject on the basis of race, sex, and ethnic background. Since Smeltertown is essentially a rural community, a "rural" control group was added to the design. This was composed of 42 subjects under 8 years of age who lived 20 km from the smelter. The test group was divided into several comparison groups for analytic purposes, but the important comparisons were generally made between the test group as a whole and the controls.

The parent(s) of each child in the study were interviewed by the project staff in order to obtain demographic, social, and health-related information. These data indicated that these groups were highly similar in their social makeup and health histories. All subjects were given a neurological and psychological examination by testers who were totally unaware of the lead status of the subjects. All examiners were bilingual and skilled at giving the tests in either English or Spanish. The tests administered to children under 6 years of age were the McSCA and the VMI. For children over six, the test battery was quite extensive. It included a WISC or a WAIS (depending on the age of the subject), the PPVT, the WRAT, the Wepman Test of Auditory Discrimination, the Oseretsky Test of Motor Development, the Bender Gestalt (Koppitz Scoring), the DAP, the California Test of Personality, and the Frostig Developmental Test of Visual Perception. The psychometric tests were done in 2 half-day sessions. The lead test group earned a mean verbal IQ of 86.86, a mean performance IQ score of 95.19, and a mean full-scale IQ score of 90.05. The comparable IQ scores for the control group were 86.94, 93.06, and 88.90, respectively. In general, analysis of variance of the data from both the neurological and the psychological examination failed to turn up any significant differences between the lead-test group and the control group. Much the same was seen on the teacher ratings of classroom behavior and the ratings of hyperactivity using the WWP.

The authors, in discussing their findings, point out that none of the test subjects, at the time of the study, were symptomatic for lead poisoning. They state that they recognize the problem of using a current marker of lead exposure to indicate previous levels of exposure. They are aware that such a practice only indicates the child's present level of exposure and does not eliminate the possibility that children in either group may have had a much higher or lower level of lead exposure in previous years. They are also aware that this one index of exposure did not indicate prolonged exposure to lead. However, the authors suggested that the scatter diagrams showing elevated levels of blood lead and of free erythrocyte protoporphyrin (FEP) at successive age levels (with different subjects at each age level) suggests that lead exposure in these children might have been chronically elevated (in the moderate range) for long periods of time. They also indicated that blood-lead levels slowly declined while FEP levels remained elevated when children moved out of the area, providing additional support for their contention that these children endured prolonged exposures to lead.

While this study failed to find neuropsychological sequelae to such exposure, the authors felt that these results should be interpreted cautiously since their test subjects were well-nourished and did not suffer from anemia. They suggest that other groups of children might be at higher risk for asymptomatic lead exposure than the sample tested in this study. They feel that one might be able to find an increased incidence of

neuropsychological sequelae in groups of children, especially toddlers, where elevated lead exposure is combined with factors like poor nutrition, anemia, and pica.

In many ways this is one of the best thought out and most reasoned studies in the literature. The authors appeared to pay careful consideration to sampling and to employing reasonable matching procedures in trying to control for all other effects except exposure to lead. They appeared to have an appropriate rationale for their testing protocol and carried it out well in terms of having "blind" examiners and assessing a number of behavioral domains. Their statistical procedures, including the use of analysis of variance techniques, was certainly adequate and represents a level of statistical execution not seen in the majority of studies in this area. Finally, their appreciation of the retrospective nature of their lead history documentation and their prudence in considering the attributes of the population they studied, as opposed to other exposed populations, in terms of risk for poor nutrition, neglect, and other factors that might mediate the neurobehavioral effects of moderate lead exposure, suggests a more sophisticated conceptualization of this problem than is usually found in the literature.

(5.) Lansdown et al.²⁸

As in the Landrigan et al. study,²⁸ the lead exposure here was presumed to be primarily due to particulate matter in the air or to lead-containing dust. The subjects were children, all under the age of 17, who lived within 500 mi of a lead smelter. All of these children ($n = 476$) had blood leads taken. The short form of the WISC or the WAIS, depending on the age of the child, and the Burt Graded Reading Test were administered to 232 out of the 275 children who were of school age. In addition, teachers completed a behavioral questionnaire on each of these children. Blood leads were also "estimated" on 105 mothers of these subjects. Results of a chi-square analysis of the total blood-lead survey showed that significantly greater numbers of children with elevated blood-lead levels lived within 400 mi of the smelter as opposed to those who lived between 400 and 500 mi from the smelter. The same relationship held up for the "estimated" blood leads on the mothers. The blood-lead survey on the school-age subjects showed that six of them had blood leads above $60 \mu\text{g/dl}$, six were between 50 and $59 \mu\text{g/dl}$, 31 were between 40 and $49 \mu\text{g/dl}$, and 131 were below $40 \mu\text{g/dl}$. The mean blood leads for this sample was $33.12 \pm 8.99 \mu\text{g/dl}$. A significant correlation of 0.18 was found for school-age subjects between blood-lead level and the distance of their residence from the smelter. However, this correlation, as pointed out by the authors, was rather small and accounted for only 4% of the variance between these two factors. Examination of the behavioral data indicated that there was no relationship between blood-lead level and IQ, reading scores, or behavior ratings. The same result was obtained when the authors compared school-age children who resided within 400 mi of the smelter at age 2 years (when their nervous system was presumably more vulnerable to insult from lead exposure) to those who were currently residing at distances greater than 400 mi from the smelter.

There are several aspects of this study which appear to weaken their case that moderate lead exposure does not appear to affect development. First of all, the assumption is again made that pertinent knowledge about the duration, dose levels, and timing of the lead exposure of those children can be obtained from one index of internal exposure. As has been mentioned frequently, this assumption is not well documented. This problem is further compounded by the fact that the index of lead exposure was obtained in many of the subjects beyond the age at which they might have been expected to be particularly vulnerable to lead exposure. This could possibly mean that these subjects were not exposed to lead at an age where it would have eventually affected their behavior. This, in turn, might indicate that a sizable proportion of this sample was essentially nonexposed to lead and that the "exposed" group, as a whole, might

have been very similar to the control group. When these factors are considered, it is not surprising that few or no differences were found between the groups.

Another possible problem in this study concerns whether the place of residence, as function of distance from the source of lead, is an adequate way of measuring the subject's exposure to airborne lead. One might assume that older children, especially school-age children, are very mobile and might be exposed to more or less lead as a function of the places they frequent other than their homes. In this case, the distance between the smelter and schools, playgrounds, and other popular neighborhood gathering places for children might be more important than residence in determining degree of exposure.

Another concern with this study is that many of the families which had moved into newer housing were known to be "problem" families. Children from these homes lived more than 500 mi from the smelter and served as control subjects in some of the data analyses. It is important to note that they served as a control group in analysis of the behavioral data on the exposed subjects who were known to reside within 400 mi of the smelter when they were 2 years old. The fact that no differences were obtained in this case cannot be interpreted strictly on the basis of a lead, no-lead comparison. Instead, the higher frequency of problems in the control families may have negatively affected the behavioral development of children in these families. This factor could have mitigated any differences that might have existed between these groups as a function of lead exposure.

(6.) Ratcliffe¹⁰

Subjects used in this study were drawn from a population of children who lived within 3 mi of a lead battery plant and who initially were part of a lead exposure survey. At the time of the survey, blood leads were obtained on all of the children in this area. Those with blood leads above 50 $\mu\text{g}/\text{dL}$ were tested again and if the high blood lead level was confirmed, they were checked by a pediatrician for signs of lead poisoning. In fact, none of the three subjects with elevated blood leads of this magnitude were considered to be symptomatic. The author therefore concluded that this sample was essentially asymptomatic for lead poisoning. Three years after this survey, 48 children were selected to undergo a behavioral evaluation. The children chosen were approximately 2 years of age at the time of the original survey. These children were grouped on the basis of their blood leads, with four boys and four girls appearing in each of the following six lead groups: below 25, 26 to 30, 31 to 35, 36 to 40, 41 to 45, and above 45 $\text{mg}/100 \text{ mL}$. The mean blood lead for these subjects was $36.5 \pm 10.4 \mu\text{g}/\text{dL}$ with a range of 18 to 64 $\mu\text{g}/\text{dL}$. The children were tested by a psychologist who did not know their lead status. Their intelligence was assessed by administering the Griffiths Mental Development Scale. This test consists of six subscales designed to measure development in the following areas: gross locomotion, personal-social, hearing and speech, eye and hand coordination, performance, and practical reasoning. In addition, all subjects were given part one of the Frostig Developmental Test of Visual Perception (this is comprised of line-drawing tasks using dots as guidelines) and a pegboard task. Analysis of the data, using "t"-tests, showed no sex differences in the blood-lead distributions or in the psychological test data. Sex was then ignored, and the subjects were split into two groups: a high-lead group with blood leads above 35 (mean $44.4 \pm 7.8 \mu\text{g}/\text{dL}$) and a moderate-lead group with blood leads at or below 35 (mean $28.2 \pm 4.7 \mu\text{g}/\text{dL}$). Analysis, using "t"-tests, failed to reveal any differences between these two groups on any of the psychological tests. A linear multiple regression analysis was conducted to examine the contributions made to variation in the IQ scores by age, schooling, mother working, number of siblings, presence of a lead worker in the family, and blood-lead levels. In general, only age of the child and schooling made signif-

icant contributions to the Griffiths IQ score. The author concluded that neither asymptomatic lead levels nor the presence of a lead worker in the home affected the developmental status of these children.

This study is quite good in comparison to many studies in this area. The author did better than most at constructing and comparing groups with different blood-lead levels. Furthermore, she was careful to select only those subjects who had been screened for lead at 2 years of age, an age where children are felt to be especially vulnerable to asymptomatic lead poisoning. The use of multiple regression analyses to examine the effects of lead against other variables is also a laudable tactic.

One problem with this study lies in the documentation of the lead exposure variable. Subjects were classified on the basis of blood leads obtained 3 years prior to the initiation of the study. The investigator argued that the exposure histories of her subjects were probably constant because of their continued residence in the same home and because of the continued presence of a lead worker in the home during the 3 years that had elapsed since the blood leads were obtained. Had she obtained a second blood-lead measure at the time of testing and confirmed her assumption, the findings would be much stronger. As it stands, one cannot be certain that the blood leads did not shift in the ensuing 3 years, creating some overlap in the lead exposure histories of the groups. While this factor does not appear to overly strain the credibility of the study there remains the possibility that there would have been enough overlap in the two groups to have negated the possibility of finding behavioral differences between them.

The behavioral testing done in this study was also far from ideal. The Griffiths is not as rigorous and as comprehensive a test of intelligence as is the Binet or the WISC. The liability of these latter two instruments as measures of deficits due to lead exposure has already been commented upon. Hence, there is some doubt as to whether the Griffiths Scales of Development was adequate for the task of assessing the neurobehavioral status of the subjects in this study. Furthermore, the use of the Frostig and a pegboard task that admittedly had no age norms hardly constitutes a thorough assessment of these subjects' perceptual and perceptual-motor abilities. In general, the neuropsychological assessment employed in this study appears to have been less than adequate.

(7.) Gregory et al.⁴²

This study sought to investigate the effects of presumed chronic exposure to airborne lead on the psychological status of children. Initially, 243 children from the vicinity of a lead ore smelter and neighboring rural areas of northern Idaho were available to the study. These children, who were between the ages of 5 and 10 years at the time the study was conducted, were placed in the experimental group if they had two blood-lead levels equal to or above 40 $\mu\text{g}/\text{dl}$ (if only one blood lead was available, it had to be $> 40 \mu\text{g}/\text{dl}$ and the subject had to have an FEP (free erythrocyte protoporphyrin) level of $> 100 \mu\text{g}/\text{dl}$). The control subjects were selected on the basis of having two blood-lead levels $< 40 \mu\text{g}/\text{dl}$ or one lead level below this plus an FEP level of $\leq 100 \mu\text{g}/\text{dl}$. The first lead levels were obtained on the children 2 months before the study was conducted and the second set approximately 2 weeks before the behavioral evaluations were done. Each of 143 experimental subjects was pair-matched with 143 control subjects on the basis of sex, age (within 11 months), SES, and length of residence in Shoshone County (either greater than or less than 12 months). Only 34 of these pairs were available for the behavioral testing. The rest had been lost to the study because the second blood lead shifted below or above 40 $\mu\text{g}/\text{dl}$ in one member of a given pair, because one or both members of the pair had congenital or physical handicaps, or because 59 subjects did not show up for the testing (39 of these subjects were in the experimental group, 20 in the control group). To enlarge the sample, 20 additional recombinant pairs were added to those already available for testing. These samples

were designated by the authors as the "Original Lead Absorption" and the "Original Control" groups.

The authors decided to resample the available subjects because so few of the original pairs were available for the evaluation. This time they used only the second blood-lead level to designate subjects as being in the experimental (lead level of $> 40 \mu/100 \text{ ml}$) or in the control group (lead level of $\leq 40 \mu\text{g/dl}$). There were 168 children who met this criterion available to the investigators. From this sample, 50 experimental and control children were pair matched on sex, age (within 4 months), and SES (within 8 points on the Hollingshead Scale). This sample was designated by the authors as the "Additional Lead Absorption" and the "Additional Control" group. Of these 50 pairs, 40 were divided into age groups in order to study the effects of lead exposure as a function of age. In this case, 10 pairs each were grouped at ages 5, 6, 7, and 8 to 9 years. This was designated by the authors as the "Age Lead" group and the "Age Control" group. Finally, 168 subjects who had at least one blood-lead determination and completed the study were reserved for some correlation analyses and designated as the "Total" group.

All subjects were tested by graduate students who had been trained in the administration of psychometric tests. The examiners tested the children without knowledge of their lead status. All subjects were administered the WISC. The primary dependent measures were the scale scores on each of the nine subtests of the WISC. The picture arrangement subtest was not administered because of the length of time required to give it. In addition, the verbal, performance, and full-scale IQ scores were used in some of the analyses.

Results of the study showed that there were no differences between the Original Lead Absorption group and the Original Control group on the subtest scores. On the other hand, a difference between groups was obtained on this dependent variable when a comparison was made between the Additional Lead Absorption and the Additional Control group. Further analysis of this data revealed that there were no specific differences between these groups on particular subtests. An analysis of variance on the IQ scores revealed that the Additional Control group had a significantly higher verbal (96.38 vs. 91.88), performance (100.86 vs. 95.94), and full-scale (98.40 vs. 93.22) IQ scores. Analysis of variance performed on data for the Age groups revealed no significant age by lead group interaction. Finally, the correlational analysis revealed that for the Total Lead group there was no significant relationship between indices of lead exposure (blood-lead levels, FEP) and subtest scores. This result was obtained whether or not the effects of SES and length of residence were partialled out of the analysis. A similar analysis on the Total groups did, however, reveal a significant negative correlation between these indices and the performance and full-scale IQ scores before and after SES was partialled out of the analysis.

In discussing their findings the authors point out a few factors, other than moderate lead exposure, that could account for the difference found between the "additional" experimental and control groups. For one thing, they suggest that differences in parental IQ, for which they did not control in the study, might account for the differences between the groups. This might have been the case, they suggest, because the less intelligent parents might have lived closer to the lead smelter and thus exposed their children to lead more than more intelligent parents. Hence, the difference in the test measures here might have been due more to parental intelligence than to a direct result of lead exposure. The second point they raise is that they found up to a 15-point spread in the mean IQ scores as a function of the tester. With such a large difference it is hard, they suggest, to give much credence to the 5-point IQ difference that occurred between the groups. Finally, there was a problem with attrition which seemed to occur

twice as often for experimental subjects. The authors suggested this might have introduced some biasing effect on the outcome of the study. They suggested that it would be difficult to make a "coherent argument" in favor of this proposition, but on the other hand, it could not be ruled out as a possibility. They concluded that the findings of the study would tend to rule out the hypothesis that major deficits occur as a function of lead absorption.

The authors point out factors which would strain the credibility of this study, mostly the IQ spread as a function of the testers and the lack of control for maternal IQ. However, there are other flaws which further damage the validity of its findings.

Poor documentation of exposure history is once again a problem. In this case, we have two recent indices of internal exposure taken within 2 months of each other. The authors assumed that these indices were representative of the entire exposure histories of the subjects because of their living close to the lead smelter, presumably for a long time. However, the reader is given no definitive information as to how long subjects resided within a reasonable distance of the smelter. About all we know is that subjects were matched according to whether they had lived in the county for under or over a year. In addition, the authors fail to give the reader any idea as to how many subjects in the experimental and control groups lived close to the smelter. One must conclude that the information provided on the distance variable is so sketchy and confusing as to leave the reader skeptical of how well the lead exposure variable was manipulated.

The manner in which the children were assessed for behavioral deficits in this study is also open to question. The tester effect on the IQ scores has already been mentioned and discussed. However, this study, more than many in the literature, seems to rely on findings from an intelligence test in determining whether or not moderate lead exposure affects the psychological and behavioral status of children. The problem here, as has been previously noted, is that such tests are probably not suited for this task since they do not measure in any depth the kinds of behaviors that might be affected by moderate lead exposure. In this case, the lack of meaningful group differences might have occurred because the measures used were too insensitive to pick them up.

Finally, something should be said about the nature of the statistically significant IQ differences that occurred between the "additional" experimental and control group. All of these differences were on the order of five IQ points. In the reviewer's judgment, differences of this magnitude at any point along the intellectual continuum would indicate that the subjects did not differ from each other in terms of their intelligence in any discernable way. So while the IQ difference is statistically significant, it appears to have little practical meaning.

d. Lead Levels in Subjects With Developmental Abnormalities

(1.) David et al.⁴²

In this study the authors sought to establish a relationship between mental retardation and moderate lead exposure. To this end, 64 mentally retarded children and 30 control subjects had blood samples taken for evidence of lead exposure when they were between 4 and 12 years of age. It must be assumed that the control subjects were of average intelligence since no IQ data were reported for this group. The mentally retarded subjects had IQs between 55 and 84 and according to their health records, had no previous blood leads greater than 50 $\mu\text{g}/\text{dl}$. Previous lead exposure data were not available for the control subjects. Both the retarded and control groups were matched on age, sex, and race. All children were presumed to come from families with equivalent social status. The birth records of the retarded subjects were surveyed. Children with at least one reported complication in their birth record, (e.g., prematurity, meningitis, eclampsia, microcephaly, or Down's Syndrome) were placed in the "probable cause" group. It was assumed that these factors were the cause of the existing

retardation. Subjects without the presence of such markers in their birth records were placed in the "unknown etiology" group. The mean blood leads for each group and the number of children in each group with blood leads above $24.5 \mu\text{g/dl}$ were the dependent measures in this study. Statistical tests ("t"-tests) indicated that the mean blood-lead level of the "unknown etiology" group ($25.5 \pm 9.7 \mu\text{g/dl}$) was significantly higher than that for either the "probable cause" group ($18.7 \pm 6.5 \mu\text{g/dl}$) or the control group ($18.8 \pm 7.3 \mu\text{g/dl}$). The latter two groups did not statistically differ from each other. A chi-square analysis of the number of subjects in each group with blood leads $>24.5 \mu\text{g/dl}$ was significant. The authors imply that this significance is caused by the increased frequency of high blood leads in subjects in the "unknown etiology" group. The authors conclude that this study demonstrates that a relationship exists between moderate lead exposure and mental retardation. They acknowledge that this finding is based on retrospective data and that missing material or omissions of pertinent data in birth records might mean that some subjects with a "probable cause" for their retardation were placed in the "unknown etiology" group. They contend, however, that such errors, if they occurred, biased the study against obtaining findings in support of their hypothesis.

This study contains a number of serious flaws which makes the finding of a relationship between moderate lead exposure and mental retardation less tenable. Perhaps the most significant flaw in this regard is the procedure of dividing the retarded subjects into a "probable cause" and a "unknown etiology" group. This grouping is crucial to the hypothesis being tested, since the authors assume that lead might have caused the retardation in the "unknown etiology" group. One difficulty with this procedure is that a lack of documentation of complications in the birth records of such subjects does not mean that the etiology of the retardation is automatically unknown and therefore possibly attributable to existing lead exposure. It is possible that social and cultural factors (e.g., growing up in an impoverished and neglectful home) might have caused the retardation. Likewise, one cannot rule out the possibility that genetic factors were the cause of the retardation found in some of these subjects. It should be noted that the reported IQ range for these groups fits well with the IQ range of children who are felt to be retarded because of cultural and/or familial factors.⁴⁴ Finally, the lack of appropriate markers in birth records does not mean that some of these children did not incur some form of brain damage during the perinatal period that might have been responsible for the later retardation. In general, it is difficult to strongly implicate lead as an associated agent without some control for the aforementioned factors.

The second point that should be made in this regard is that birth complications, whether taken singly or in clusters, have been demonstrated in several studies *not* to be predictive of the later physical and/or mental status of children.^{46,47} Therefore, assigning an organic cause for retardation based on such markers may lead to an erroneous assignment of etiology for the retardation. Thus, the distinction between the "probable cause" and "unknown etiology" groups becomes very problematic and possibly invalidates the manner in which the hypothesis of the study was tested.

Mention should be made of how the retrospective nature of this study also clouds the interpretation of the data. The lead histories of the retardates is sketchy and raises the inevitable questions about differences in the exposure histories of the two groups. Moreover, to select a group of retardates and presume that early lead exposure played a significant role in the retardation of the subjects is certainly not the best way to identify a relationship between mental retardation and lead exposure. Such studies, to be well executed, should be done prospectively. They should select children who are exposed to lead early in their lives to varying degrees and for various lengths of time. The range of lead exposure in these children should then be related to later intellectual outcome both on its own account and by taking into account the possible concommi-

tant role played by other important social and health factors. Only in this manner can the nature of the relationship between lead exposure and later mental retardation be clearly elucidated.

A further problem with this study is the fact that the sample of children studied represents the characteristics of only a segment of the population of retarded children in this country. Therefore, the conclusions drawn from this study should only be generalized to groups of retarded children with similar characteristics. If the investigators wished to make broader statements about the relationship between lead and mental retardation, they should have sampled other representative segments of this population.

Finally, poor statistical procedures plagued this study. Again, multiple t-tests were performed on the data when the use of an analysis of variance would have been more prudent and more appropriate. In any case, the mean blood leads of the "unknown etiology" group and the other two groups fell in the normal range⁴⁵ and the difference between the three groups on this measure, while statistically significant, is so small as to make one wonder if it has any practical meaning. In the chi-square analysis of the data, the blood-lead range was divided into successive classes on the basis of a 10 $\mu\text{g}/\text{dl}$ interval. The frequency of children in each etiologic group who fell into each of these blood-lead intervals was then examined. This analysis showed that significantly more subjects in the "unknown etiology" group, in comparison to the two other groups, had blood lead levels $\geq 25 \text{ mg}/\text{dl}$, with the bulk of these subjects having blood lead levels between 25 and 34.5 mg/dl . The cut-off point marking the beginning of the exposure range, 25 mg/dl , used by these authors was below that of 30 mg/dl recommended by the current CDC guidelines. It would be of interest to know how many of the subjects in the "unknown cause" group would have been labeled as "moderately exposed" if the CDC guidelines had been used. In any case, if one combines the control and "known cause" subjects together and uses this as a control group, one finds that 15 (28%) of the "unknown etiology" and 12 (25%) of the "controls" have blood leads $\geq 25 \mu\text{g}/\text{dl}$, which is hardly a major difference.

(3.) David et al.⁴⁶

In this study the authors tried to establish a link between hyperactivity and moderate lead exposure. Blood- and urine-lead levels were obtained for a group of hyperactive and a group of nonhyperactive children. The hyperactive children were diagnosed on the basis of ratings made by teachers (using the Conners Scale), by parents (using the WWP), and by physicians. The hyperactive subjects were also divided into "pure" ($n = 54$), "possible cause" ($n = 11$), and "probable cause" ($n = 9$) groups on the basis of data in the subjects' birth records. The "possible" and "probable" cause subjects each had some kind of birth complication(s) reported in their records. These complications were felt to signal the possibility of damage to the CNS. The difference between the two groups was that more severe forms of birth complications appeared in the records of "probable cause" subjects. Subjects at the time of the study had a mean age of 7 ± 2 years. The mean blood lead for the "pure" group was 26.43 $\mu\text{g}/\text{dl}$, for the "possible cause" group 29.95 $\mu\text{g}/\text{dl}$, for the "probable cause" group 22.89 $\mu\text{g}/\text{dl}$, and for controls 22.16 $\mu\text{g}/\text{dl}$. A positive control group consisting of lead-poisoned children ($n = 8$) had a mean blood lead of 41.06 $\mu\text{g}/\text{dl}$. Urine-lead levels obtained 24 hr after the administration of penicillamine were 144, 189, 46, 77, and 325 mg/l of urine, respectively. Comparisons made by "t"-tests showed that for both indices of lead exposure, the "pure", "possible cause", and lead poisoned subjects differed significantly from the control and the "probable cause" groups. In both instances, the "probable cause" group did not differ from the control group. Finally, a chi-square

analysis was done on the number of subjects in each group who had blood leads above 24.5 mg/100 ml. This analysis was significant, indicating that many more "pure" hyperactive subjects (53%) than controls (23%) had leads above this level. The same pattern was found in a chi-square analysis on the number of subjects in each group with urine leads above 80 mg/l. The authors concluded that the findings showed a relationship between moderate lead exposure and hyperactivity, albeit the relationship was not established as being one of cause and effect.

This study suffers from many of the same flaws mentioned in the critique of the previous study done by this research team. Specifically, these flaws were the retrospective nature of the experimental design, the inadequate documentation of the subject's lead history, and the way in which subjects were selected to be in the "pure", "possible cause", or "probable cause" groups.

Another major problem with this study, however, is a lack of a clear-cut definition of hyperactive behavior. This is a problem that plagues much of the literature on this problem. Children are labeled or diagnosed as being hyperactive on the basis of criterion behaviors which shift from one diagnostician to the next. It is difficult to draw any inference between possible etiologic factors (like lead) and this diagnostic category when the nature of the behavior defining the category varies from observer to observer or from test measure to test measure. In this study we can be certain that the definitions used by the three sets of raters were not the same since each set of raters, i.e., parents, physicians and teachers, used a different rating instrument to rate the same child for hyperactive behavior. For example, it appears that the physicians used their own judgments in diagnosing these children whom they probably knew quite well. Moreover, the Conners rating scale used by the teachers rates the child on aggression, behavior problems, and other emotional disorders, along with overactivity. Thus, a melange of behaviors (acting out, hostility, aggressiveness) may have been measured along with overactive behavior. Therefore, we cannot be sure what was really wrong with these children. Problems like this could have been avoided by having trained observers blind to the lead status of the subject take direct measures of these children's activity levels in different situations, e.g., at school or at home.

Mention should be made of a few other problems that strain the credibility of the study. For one thing, the sampling procedure resulted in a narrow sample. It is hard to imagine that this population of hyperactive children, drawn from a clinic primarily serving economically deprived ethnic groups, is representative of the hyperactive population in any general fashion. More adequate sampling would be required if such findings were to have more generality. Another problem was that the number of subjects in some of the hyperactive subgroups was so small as to make one doubt the reliability of the data that was obtained. Finally, it might have been more appropriate to have applied an analysis of variance to the group blood-lead levels and urine-lead data and then, if significance was obtained, do the appropriate group comparisons using "t"-tests.

(2.) David et al."

In this study the investigators sought to add further credence to previous findings that there might be a strong relationship between moderate lead exposure and hyperactivity. In this case they examined the effects of chelation therapy on hyperactivity in a group of children with no known cause for their hyperactivity ($n = 7$) and in a like group of children with a probable cause for their hyperactivity ($n = 7$). The diagnosis of hyperactivity and assignment to the "unknown cause" or "probable cause" groups was much the same as in the previous study. All children in the study had blood leads greater than 24.5 $\mu\text{g}/\text{dl}$ and urine leads of greater than 80 mg/l of urine. The mean blood lead for the "unknown cause" group was 29.2 $\mu\text{g}/\text{dl}$ and 22.5 $\mu\text{g}/\text{dl}$ for

the "probable cause" group. The mean age of subjects in the study was 8.2 years with a range of 6 to 10.5 years. All subjects underwent a 4-week course of chelation treatment with penicillamine (except for two allergic subjects in each group who were given CaEDTA). There followed another 4 weeks where no treatment was administered. Those subjects whose blood-lead values returned to baseline levels (five experimental and three control subjects) were given another 4-week course of treatment. In addition, four subjects (one in the "unknown cause" and three in the "probable cause" group) were started on a course of methylphenidate at the beginning of the therapy. They were started on a low dose and titrated up to a dose of 40 mg/day over the 12-week period of the study. A teacher rating scale (Conners), a parent symptom questionnaire (Conners), a hyperactivity checklist (the WWP), and a clinical global impression scale were administered during the drug-free baseline period and at the end of the study.

Results of the study showed that the blood leads went down for both groups during the initial administration of the chelating agents: 9.9 $\mu\text{g}/\text{dI}$ for the experimentals, 4.5 $\mu\text{g}/\text{dI}$ for the controls. The "unknown cause" group showed significant improvement, as opposed to controls, on the teacher rating scales. Both groups, however, improved significantly on the hyperactive checklist done by the parents. On the parent symptom questionnaire the experimental group, but not the controls, improved significantly on the dimensions of impulsive-hyperactivity, learning problems, and conduct problems. The "unknown cause" group, but not the controls, also showed significant improvement on the global clinical impressions scale. The authors suggested that these findings showed that chelation improved the hyperactive behavior of the "no known cause" group. They felt that this strengthened the contention that there is a significant relationship between moderate lead exposure and hyperactivity.

This is certainly an interesting study. However, its implication of lead as an etiologic factor in hyperactivity seems weak. The fact that the lead exposure histories of the subjects are again not well documented plus the aforementioned problems with assigning "cause" on the basis of material in birth records to a behavioral entity like hyperactivity weakens this study. Of course the groups seemingly did differ in response to the therapy employed in the study. This effect, however, was confounded by use of different chelating agents and by the use of methylphenidate in some of the subjects.

There are at least four additional areas upon which to seriously question the validity of the study. For one, the size of the samples is so small that it would be hard to have much faith in the reliability of the findings. Secondly, it would appear that the pre- and post-treatment assessments were not done by observers who were "blind" to the health status of the youngsters. This might have well have created a "halo" effect in terms of the observers' expectation of differential improvement in the experimental subjects. This might have biased the ratings of improvement in favor of the "unknown cause" group. Moreover, one cannot rule out the possibility that the subjects in the "unknown cause" group had greater expectations than those in the "known cause" group of improving their behavior because of the treatment. This factor might have altered their behavior far more than the drug. These problems, which seriously impair the study, could have been avoided by the use of "blind" raters and by the incorporation of "unknown cause" and "probable cause" placebo groups into the design of the study. Thirdly, it is unclear, based on the published report, what constituted "improvement". Both groups improved on at least one scale, so how does one judge which measures decide that one group improved more than the other? It also appears that each of these scales measures somewhat different aspects of behavior. Therefore, a variety of behaviors, not just high activity levels, were assessed. One then has to ask how improvement in "compliance" or in "learning" constitutes a reduction in hyperactivity. Finally, the statistical procedures used to test the response are not clear. A

very large number of "t"-tests were run on this data, thus spuriously inflating the chances of obtaining significant findings. More appropriate procedures, like analysis of variance, might have been initially applied to the data to see if the use of *post hoc* tests were warranted by the data.

(4.) Pihi and Parkes⁴⁴

This study examined the relationship between exposure to various heavy metals and learning disabilities. The degree of exposure was measured by the concentration of these metals in head hair. The concentrations were compared for a group of 31 children with learning disabilities (LD) and a group of 22 controls. Subjects in both groups came from a sample of 1030 regular fourth graders. All of these children were administered the Pupil Rating Scale which tests skills like auditory comprehension, spoken language, and motor abilities. The 226 children who scored below 67 on this test were administered the PPVT and Metropolitan Achievement Test (MAT), which measures skill levels in reading, spelling, mathematical computation, and mathematical problem solving. Those children who scored at least average on the Peabody and who failed at least one subtest of the MAT were designated as LD subjects. Normal controls were randomly chosen from the sample of fourth graders who had scored above 67 on the Pupil Rating Scale. Both groups were matched on age, sex, socioeconomic status, and native language. Hair was collected from each subject and analyzed for concentrations of 14 metals. An analysis of variance indicated that the LD group was significantly higher than the control group on concentration levels of seven of these metals: sodium, cadmium, cobalt, lead, chromium, manganese, and lithium. To test the possibility that other organismic variables might have accounted for the variations in trace metal content, a regression equation was developed for each metal using age, sex, socioeconomic status, language spoken, and group (LD or control). As predictor variables, only sex and group membership proved to be predictors of metal content. A discriminant function analysis indicated that the concentration of five metals (cadmium, cobalt, manganese, chromium, and lithium) successfully predicted the classification (LD or normal) of subjects with a 98% accuracy. Lead was not included in the prediction equation only because the predictive function of this element was well served by cadmium and cobalt. The authors concluded by suggesting that further research in this area might be useful in providing information about the etiology of LD as well as possibly proving to be fruitful in the diagnosis of such problems.

Whether this study really shows that there is a relationship between trace metal concentration, specifically of lead, and learning disabilities is open to question. Hammer et al.⁴⁵ report that mean normal hair-lead levels fall in the range of 6 to 10 ppm, while hair-lead concentrations obtained from fourth-grade school boys living in a lead and zinc mining and smelting community ranged as high as 600 ppm with a median of 52 ppm. By this standard, the controls (4 ppm) in the present study appear to have been unexposed while the LD group (23 ppm) may have been subjected to some degree of lead exposure. The problem here is the lack of information concerning how hair-lead concentration translates to a more commonly used measure of exposure.

Another problem area in this study pertains to the selection of the LD children. This is a very difficult diagnostic entity to define. The investigators for the most part used a standard educational technique of classifying such children (at least average IQ and at least a 1-year lag in a defined academic skill area). However, it would appear that this group of children had a variety of potential disabilities such as auditory comprehension problems and poor motor skills, any of which might have interfered with learning. Hence, it appears difficult to clearly define the problems that these children exhibited. As the authors themselves recognized, it would be difficult to specify which of several possible cognitive and academic deficits were possibly the result of exposure

to these metals. Improved definition and measurement of learning disabilities leading to a more homogeneous classification(s) of the problems LD children have is the only way of making such investigations yield more interpretable data.

(5.) Beattie et al.⁷⁰

The goal of this study was to demonstrate that lead exposure, as measured by concentration of lead in soft water in certain sections of the city of Glasgow, had a strong link to mental retardation. To this end, 154 children were selected for study. Half of these children, the test group, were retarded (i.e., they had IQ scores of 70 and below on either the Griffiths or on the Binet) and the other half of the subjects, the control group, had normal intelligence. The cause of the mental retardation could not be documented in either the birth or the health histories of the test group. Both groups, at the time the study was conducted, had a mean age of 4.07 years.

The place of residence of the subjects' mothers during pregnancy and the children's residence during the first and second 6 months of his/her life was obtained. The water concentration of lead, measured in the first sample of cold water drawn from the tap in the morning, served as the primary dependent measure in this study. This measure was taken in each place of residence for subjects during the times mentioned above. This measure was deemed as critical because prior research had indicated that this was the water that was used in the dried feed preparations of the infants' food each morning. Mean concentrations of water lead were presented for the test and control subjects during each trimester of pregnancy, during the first 6 months of life, and during the second 6 months of life. The overall mean water-lead concentration for the test group was $379 \pm 416 \mu\text{g/l}$; for the control group it was $223 \pm 198 \mu\text{g/l}$. At each period of development, the water-lead concentration of the test group appeared to be roughly one third higher than that for the controls. Measures of internal exposure, blood levels of lead, were taken on 30 of the test subjects at the time the study was conducted. None were taken on the controls. Instead, the "control" blood-lead data came from children hospitalized for diseases not related to lead exposure. In terms of measures of internal exposure, the 30 test subjects had mean blood-lead level of $35.4 \pm 12.1 \mu\text{g/dl}$, and the "controls" had a mean level of $17.8 \pm 4.9 \mu\text{g/dl}$. Unfortunately, no statistical analysis of either mean water- or blood-lead concentrations were presented in this report. For the primary analysis, the overall concentration level of lead in water was broken down into the following gross ranges: 0 to 399, 400 to 779, and $>800 \mu\text{g/l}$. The control and test subjects were presumably matched on a pair-by-pair basis on age, sex, and geographic area of residence. In all, there were 64 such pairs on whom water-lead level concentrations were available. Water-lead concentrations above 800 mg/l were found for 17% of the test cases, but none of the controls. There were 43 pairs of subjects whose water-lead concentrations fell in the same range. It was argued by the authors that if there was no relationship between mental retardation and water-lead concentration, about half of the remaining 21 pairs would be expected to have a matched control with a higher water-lead concentration than the paired test subject. In fact, this only happened in six pairs. A binomial distribution was made on this data. This distribution yielded a significant difference indicating, according to the authors, a significant relationship between mental retardation and water-lead concentration. Using Bayesian statistical tests, the authors determined that children exposed to water concentrations of lead above $800 \mu\text{g/l}$ had a higher probability of being retarded than the child whose drinking water concentration of lead was unknown. The authors concluded that the study showed that there was an association between water concentrations of lead and mental retardation. Whether this association was one of cause and effect could not, in their estimation, be determined from the study. However, the authors did feel that this was an important finding since this potential health hazard could be eradicated.

The authors chose to limit their conclusion to indicating that there is a relationship or association between water-lead concentration and mental retardation. A number of factors, however, make even this conclusion suspect. One problem, in this regard, is their reasoning that if nothing in the health records of the retarded subjects suggests a cause for their malady, this must leave lead exposure as a possible etiological candidate. What these authors seemingly neglect to consider is that these children could have been retarded on genetic grounds and/or by reason of growing up in very impoverished and perhaps neglectful environments. Moreover, the absence of reported birth complications and other health problems in the records of the retarded children does not automatically rule out the possibility that some of these children did sustain their retardation because of perinatal brain damage. The fact that the control subjects growing up in the same area of the city did so well could indicate that the control subjects possibly came from families where there was more concern about their welfare. Information on maternal IQ, sibling IQ, family educational and occupational status, family rearing attitudes, and family health would have been useful in clarifying whether these factors or lead exposure were more closely associated with the retardation of the test group subjects. Without such information, the effect of lead as an associative factor in the mental retardation of the subjects is greatly weakened.

Another weakness in this study is the difficulty one has in translating the various concentrations of lead in water into recognizable internal indices of lead exposure (e.g., blood-lead levels) since the reader is given no information about this issue. Furthermore, questions like the reliability of the morning tap lead measure and its stability over a 5-year period are not addressed in the study. Finally, this study is basically retrospective in nature and does not, except for the first year of life, offer any information regarding the way in which these children might have been exposed to lead over the course of their lives up until the time of the study. Thus there is no way of knowing the degree to which these two groups actually differed on the variable of lead exposure beyond the first year of life. This problem is heightened by the lack of comparison of blood-lead values between control (the original control subjects) and test group subjects. The data that are provided (using pseudo-controls) are really not useful for this purpose.

Finally, there are problems with the statistical aspects of this study. Fundamental statistical analyses of the water-lead concentrations for each group as a function of residence during pregnancy and the first year of life are not reported. Likewise, no statistical analysis was done on the overall mean water-lead concentrations for each group. Therefore, the reader has no way of knowing whether differences in exposure were actually occurring between the groups during this period of time. Conversely, the way in which the authors did statistically test for differences in water-lead concentrations between the groups seems baffling. No rationale was provided for the selection of cutoffs for each range of water-lead concentrations (which appear to be rather large). Moreover, the fact that the test of their hypothesis was made on only one third of the available subjects is disconcerting. One has to wonder if a significant relationship between mental retardation and water-lead concentration would have been found if more appropriate statistical procedures were applied to *all* of the water-lead concentration data.

(6.) Youroukos et al.^{20a}

These authors investigated the possible relationship between lead exposure and mental retardation. Comparisons were made on measures of blood-lead levels and δ -ALAD activity between an experimental group of 60 retarded children of "unknown etiology" (41 had cerebral palsy, 33 had epilepsy, and 23 had some combination of these two disorders) and control groups of 30 retarded children of known etiology (e.g., disor-

ders like P.K.U. and Down's Syndrome) and 30 children with average intelligence. The children in both retarded groups resided in the same institution for approximately 2½ years. The mean age of the subjects in all three groups was approximately 8.5 years. Sex was controlled by having equal numbers of boys and girls in each of the three groups.

Results showed that the experimental group had a significantly higher mean blood-lead level ($30.0 \pm 11.4 \mu\text{g/dl}$) than did the mentally retarded ($20.8 \pm 6.9 \mu\text{g/dl}$) and the normal controls ($20.9 \pm 6.9 \mu\text{g/dl}$). It was also reported that 14 of the experimental subjects (23.3%) had blood-lead levels above $40 \mu\text{g/dl}$ in comparison to only 1 retarded control (3.3%) and none of the normal controls. Results for the δ -ALAD measure showed that the 14 experimental subjects with blood-lead levels in excess of $40 \mu\text{g/dl}$ had significantly decreased δ -ALAD activity in comparison to the other two groups. Likewise, 13 experimental subjects (21.7%), in comparison to 4 mentally retarded control subjects (13.3%), had significantly reduced δ -ALAD activity as defined by the lowest value obtained for the normal controls ($533 \times 10^{-3} \mu\text{mol}$ of PBG per milliliter of RBCs per hour). No significant differences in the blood values of experimental or control subjects were found as a function of urban vs. rural residence. The authors concluded that the finding of significant lead exposure in more than 20% of the experimental subjects was important because lead might have been the etiological factor in their retardation or because lead may have aggravated their existing retardation.

The composition of the experimental group poses a problem. The subjects in this group were said to have mental retardation of "unknown etiology". However, the majority of subjects in this group were reported to have handicapping conditions caused by CNS damage. In addition, they had the kinds of handicapping conditions that often have mental retardation associated with them as a result of the underlying CNS disorder. Thus, it is difficult to understand how these children could have been classified as having mental retardation of "unknown etiology" any more than the mentally retarded control group who had a "known etiology" for their intellectual handicap. The likelihood that the etiology of the experimental subjects' mental retardation was some form of CNS damage or pathology would seriously weaken the hypothesis that the increased lead exposure found in these subjects might have been an etiologic factor.

The possibility still exists that the increased lead exposure of subjects in the experimental group aggravated or increased their degree of retardation. However, this issue is in no way addressed in this study since the investigators did not provide any IQ data which would have indicated that these subjects were in some way intellectually inferior to the mentally retarded controls.

Another problem with this study is the lack of definitive information regarding the intellectual development and history of lead ingestion of the subjects in the two retarded groups. Lead ingestion, in the form of pica, is not an uncommon habit in children who are seriously retarded for reasons other than lead exposure. Thus one cannot know from the information given whether the increased exposure in the experimental subjects occurred before their retardation (or before their condition became worse) or after their intellectual handicap was established. The authors felt that they controlled for pica by the fact that the subjects in both of these groups came from the same institution and that some in each group were reported to have engaged in pica. This is insufficient as a control procedure. What needs to be known is whether there was any difference between these groups in terms of the number of children who engaged in pica at the time of the study and in terms of histories of pica predating intellectual decline.

A final problem with this study is that it is basically a retrospective design with respect to the lead exposure history variable. The investigators were cognizant of this

and chose to handle this problem by using RBC δ -ALAD activity which they report as being depressed "for years after exposure to lead." This tactic was potentially a strong point for the study. However, the authors compromised it by comparing the level of activity of this enzyme in only those experimental subjects who had blood-lead levels in excess of $40 \mu\text{g}/\text{dL}$ against activity of the enzyme in all control group subjects. This procedure raises the question as to whether significance on this dependent measure would have been found if the total experimental group had been used in this comparison. In addition, data showing low blood-lead levels (12 to $18 \mu\text{g}/\text{dL}$) in four retarded control subjects with significantly decreased levels of δ -ALAD activity cast some doubt on the reliability of δ -ALAD as an index of chronic lead exposure.

2. Overview of Common Procedural Problems

The primary assumption of studies of so-called asymptomatic lead poisoning is that sustained levels of moderate lead exposure eventually interfere with the behavioral and intellectual development of children with such exposure histories. In order to adequately study this question, it is essential that the investigator document the lead exposure history variable in his or her subjects in such a way that we know that there is a reasonable separation of exposure levels between the experimental and the control groups. It is also important that the investigator, when documenting the exposure histories of his subjects, provide pertinent data regarding when the exposure occurred; i.e., at what age was the child exposed, how long the exposure continued at elevated levels, and some estimation of the dosage or level of lead intake incurred by the child at any given time. This information is necessary to answer critical questions regarding whether the timing of the exposure is important and whether there is a dose-duration effect on later development.

The major flaw in most studies in this regard is that they all used essentially one measure, usually blood lead, to assess the exposure histories of their subjects. In some cases, the index of exposure was obtained at or close to the time that the behavioral testing was done on the children. The assumption made here was that the current marker of lead exposure adequately measured the entire exposure history of the subject up until the time that he or she was tested. However, with one exception,⁶¹ none of the studies reviewed gave any evidence that would support this kind of assumption. Therefore, it is impossible to be certain that the subjects in the "exposed" and "nonexposed" groups actually differed to any appreciable degree in lead exposure history. Indeed, there is always the possibility that in some of these studies the two comparison groups could have had a considerable degree of overlap in their lead exposure histories.

The assumption that one marker of lead exposure can be used to reliably index the child's entire exposure history was seriously challenged in studies where subjects were selected on the basis of an index of exposure, usually in a neighborhood lead screening program, often obtained several years prior to the behavioral testing. In some of these studies^{53,55,56,58} the blood-lead levels obtained at the time of behavioral studies had changed substantially from what they were at the time subjects were initially assigned to experimental or control groups. In this case, exposed subjects often showed decline in blood-lead values, sometimes far into the "safe" or normal range as delineated by the CDC guidelines.⁴⁵ Conversely, some of the control group subjects showed increases in blood-lead values, often up into the so-called asymptomatic range. This shift in blood-lead values creates the suspicion that the lead history of the subjects in these studies were not adequately indexed by the use of a single measure. It also creates a degree of suspicion that the experimental and the control groups could have been somewhat similar in terms of their exposure histories. Ordinarily this factor would decrease the possibility of finding lead effects on behavior that might have been obtained if

more attention had been paid to insuring that the groups were well separated on this variable. This appears to have possibly happened in some of the studies herein reviewed.^{44, 48, 53} In some cases, however, lead effects were obtained in spite of evidence that these groups were probably not well separated on this variable.^{51, 55, 56, 58} The fact that this happened in these studies might be viewed as indicating that the lead effect was indeed a potent influence on the obtained behavioral outcomes. The credibility of this interpretation rests on how well the investigator controlled for the effects of other influential variables (such as parental caretaking practices) and on how well other aspects of the study were executed.

It is also important to note that assessing lead exposure in this manner does not give any indication as to whether a child is suffering from a short-term, high-level dose of lead intake or whether the child has been ingesting small amounts of lead over a long period of time. The problem of differentiating level of dosage and duration of intake is difficult, but it is of central importance to any investigation of the effects of moderate levels of lead intake over time. It is possible, for example, that an elevated blood lead in the so-called asymptomatic range may reflect a very brief exposure at a high dosage which may not have any behavioral aftereffects. On the other hand, most investigators are concerned about intake at moderate doses that over a long period of time may have an insidious effect on the development of the child's CNS. Without repeatedly measuring blood-lead levels, the specific exposure history cannot be accurately determined in this regard.

Finally, a word must be said about the problem of the age at which the lead burden occurs. Some reviewers and investigators in this area have suggested that it is important to know if peak lead exposure and resultant elevation in lead burden occur during the first 2 to 3 years of life, a time when the developing CNS might be unusually vulnerable to lead insult. The majority of the studies reviewed did not appear to be concerned about the timing of exposure in the child's life.

Another problem in these studies is defining what constitutes a moderate level of lead exposure. In almost all of the studies reviewed, the primary index of exposure was micrograms of lead per 100 ml of whole blood. However, there was no uniform definition, using this measure, of the upper and lower boundaries that clearly defines the range of "asymptomatic lead poisoning". For example, some investigators have implicitly defined the upper limit of asymptomatic lead poisoning as 100 $\mu\text{g}/\text{dl}$ in the absence of any clinical signs of encephalopathy.^{48, 54} However, other sources,⁴⁹ including the 1978 guidelines set by the Center for Disease Control,⁴⁵ consider a blood level of 70 $\mu\text{g}/\text{dl}$ to be indicative of lead poisoning regardless of the presence or absence of clinical signs. Equally bothersome is the fluctuation of what constitutes the lower limit for so-called asymptomatic lead poisoning. In the studies reviewed, this boundary varied from 24.5 to 40 $\mu\text{g}/\text{dl}$ of whole blood in spite of the fact that one authority in the field,⁷¹ as well as the 1978 CDC guidelines,⁴⁵ have suggested that any blood-lead level above 30 $\mu\text{g}/\text{dl}$ constitutes a potentially damaging level of lead for children and adults.

Questions have been raised regarding the adequacy of blood lead as a measure of exposure. This is especially the case when one blood lead or two blood leads taken relatively close to each other (within 6 to 12 months) were used to index the entire exposure history of the child. Problems with this kind of practice have already been noted. Some investigators have tried to obtain a better idea of the exposure history of the child by utilizing other measures that are felt to be good indices of prolonged lead exposure. Measures typically used in this manner include dentine-lead concentration and X-rays which indicate the presence of epiphyseal lead lines. However, there are some grounds for questioning the validity of these measures as indicators of lead exposure, especially prolonged exposure. For one, Chisolm⁷¹ has suggested that data indicate that the accumulation of lead in bone tissue may not accurately reflect lead

burden in soft tissues of the body. This is important because the lead effect of interest in most cases is that caused by excessive burden in the soft tissues of the body, most notably the brain. A further difficulty posed by the use of these measures is that heightened values, in the absence of other evidence, fail to indicate when the exposure occurred (that is, the timing of the exposure) and whether the accumulation of lead in the body occurred at dosages high enough to be of concern. Another difficulty with these measures, especially dentine, regards the relationship between these indices and blood lead. In this case, blood lead is an index of exposure that is commonly used in the literature. Meaning, in terms of risk of injury from lead exposure, appears to be generally established for blood-lead levels. The same does not appear to be true for dentine-lead concentration or for epiphyseal lead lines. It is often the case that dentine-lead concentrations are reported without any reference to what these levels of concentration mean in terms of the more commonly used blood-lead measure.^{50, 51a, 52} This makes it hard to interpret this information since it cannot be related to a currently meaningful and established index of exposure.

This brings us to the question of what the best measure of moderate exposure might be, given all of these problems. Chisolm, in his review, suggested that serial urine levels of lead after the ingestion of chelating agents (e.g., EDTA) would provide the most ideal measure of body burden.⁷¹ However, ethical considerations involved with chelating children whose blood levels of lead are below a certain point, usually 80 $\mu\text{g}/\text{dl}$, make this measure less than ideal. These considerations, along with economic ones, would be compounded in a prospective study where frequent measures of lead levels would be required. In light of this, possibly the best compromise would be to use multiple measures of blood-lead levels across a span of time. However, none of the investigations reviewed did this. Most relied on just one measure of lead burden, usually using blood-lead level, either by itself or in a combination with other measures.

Another set of difficulties common to many of these studies relates to the selection of subjects. Problems were frequently encountered in selecting subjects on the basis of the presumed exposure to a source of lead, on the basis of diagnostic entities that were not well defined, or without due concern for the adequacy of the sampling procedures employed.

Source of exposure was used in several studies to identify the experimental and control subjects. The problem with this procedure is that in most instances the source of the exposure was not carefully defined and in the end, this variable often seemed to bear little relationship to the actual measures of internal lead exposure.

Pica for lead-containing substances was frequently the way "exposed" subjects were identified. None of the investigators who used this means to identify test subjects attempted to define what they meant by pica in terms of crucial considerations such as how frequently it occurred in a given child, how much was ingested in a certain time period, and how long and at what age the child had pica for lead-containing substances.⁵⁵⁻⁵⁷ Most of the investigators relied on interviews and questionnaires to determine if the children had pica.^{55, 56, 58, 65} In all cases, the reliability of this information, much of it historical, was not checked. This oversight is of some importance since in one study some mothers who had at one time indicated that their children engaged in pica later, in a follow-up study, denied that their children had done so.⁵⁵

Two other indices for sources of lead exposure have been used. One is old housing and the other is automotive exhaust or airborne lead particles. In the first instance, no precise definition was given as to what constitutes "old housing". Presumably this meant houses with peeling lead-based paint. In some cases, residing in an old house did not discriminate exposed and nonexposed children based on their blood-lead levels. The important point here is that while it would be expected that children from old housing with unstripped lead-based interior paint would have a higher lead exposure

than children living in newer housing, this fact alone cannot be taken as evidence that they actually differ. Old vs. new housing could very well be used as a source of high risk vs. low risk for lead exposure subjects in a prospective study, but longitudinal records of blood-lead level or some other reliable index of internal exposure must serve as the criteria that define the actual exposure histories of such subjects.

With respect to airborne lead exposure, one study claimed that subjects had been exposed to lead by way of automobile exhaust, but the method used to identify these subjects and a definition of how lead in the exhaust was measured was not presented.⁵² Two other investigations have defined airborne lead exposure in terms of the distance that the children lived from a smelter that emitted lead into the air. One showed a significant but very low correlation ($r = 0.18$) between distance from the smelter and blood levels of lead.⁵⁹ In the other study, distance from the smelter did not differentiate children on the basis of their blood-lead levels except for a small number of exposed children with elevated blood levels who continued to reside close to the smelter.⁵⁸

One problem with studies that investigated the "distance" variable was their use of the child's place of residence to measure this variable. This practice fails to account for the fact that children, especially school-age children, are very mobile. A child's exposure to lead might be dictated more by where the child goes to school or where the child spends his/her leisure time than by the child's place of residence. Failure to take this into account may be one reason why the distance variable did not show any strong relationship to measures of internal lead exposure.

Finally, mention should be made in this context of lead-containing dust as a potential source of exposure. It could be that exposure via this route is quite pervasive because it can be inhaled or ingested when the infant or young child engages in any form of hand to mouth activity. None of the studies reviewed looked at this as a potential source of exposure. It might be, though, that direct measures of this form of lead contaminant in the child's home and play environment might prove to be a precise way of selecting exposed and nonexposed subjects.

Other problems were encountered in studies where experimental subjects were selected for study on the basis of belonging to a given diagnostic category (e.g., mentally retarded, hyperactive, LD). The main difficulty here is that some of these diagnostic entities, especially hyperactivity and LD, are not precisely defined in the literature. Because of this, the children so labeled usually have a variety of disorders other than just being overactive or unable to learn. The procedures used in the reviewed studies to diagnose these two classes of children also appeared to measure a broad range of behaviors. This was the case in two studies examining the relationship between lead exposure and hyperactivity where three different rating scales tapping three different dimensions of behavior were used to select subjects.^{65, 67} The problem here and in other studies like it is that it is hard to know which behavior or set of behaviors, if any, is associated with moderate lead exposure.

The other procedural difficulty encountered in this regard had to do with the examination of birth records and health-related materials to determine if early pre- or post-natal factors were responsible for the mental retardation or hyperactivity of the child. These materials were used to select children who presumably had no obvious cause for their malady. Their blood-lead levels were compared with a group of children with a known or assumed cause for their disorder as determined by the same kind of records. Lead exposure was then implicated as a possible etiologic factor if the blood-lead level of the "unknown cause" group was significantly higher than that for the "known cause" group. As pointed out frequently, the unreliability of information recorded in birth records, plus the lack of predictability that such information has with respect to later developmental outcomes, makes such a strategy of dubious value in testing for the relationship between moderate lead exposure and diagnostic entities like mental retardation and hyperactivity.

Finally, the method of sampling subjects in these studies was often quite restricted with respect to important characteristics like race, social class, place of residence, place of schooling, etc. The net effect of such procedures was to severely limit the generality of the findings. However, many investigators seemingly overlooked this fact by concluding their papers with a set of generalized statements regarding the effect of lead exposure on some aspect of behavior.

Another major area of difficulty in these studies involved the tasks that were used to assess the neurobehavioral effects of lead. Most of the issues revolve around task selection. Many studies relied on IQ tests to assess their subjects. As mentioned previously, such tests typically sample a wide variety of abilities and skills. IQ tests generally do not specifically measure in any appreciable depth particular skills like perception or memory that are important determinants of intelligence. Thus, the IQ score is probably not sensitive enough to pick up deficits caused by the effect of lead exposure on the CNS in skills that mediate some kinds of intellectual behavior. Another problem was that many investigators also overlooked the well-documented fact that many of these IQ tests are culturally biased against certain ethnic groups (often those very groups who were also at increased risk for elevated lead exposure) and failed to account for this when interpreting their data. Finally, investigators seemed to ignore the fact that the race of the examiner can also negatively influence performance on IQ tests if it differs from that of the child. The latter two problems are particularly important when one considers studies where subjects or groups were not matched and the children were heterogeneous in terms of their racial and economic background.^{52,65}

One of the most glaring weaknesses in all of these studies is the apparent lack of a clear-cut rationale for the selection of their behavioral measures. In some studies it appeared that the behavioral measures were chosen because they were readily available to the investigator.^{52,55,57} In other cases an implicit rationale was utilized in the sense that the tests selected were thought to be sensitive to behavioral deficits usually associated with brain damage. In instances where this was done, measures of motor, perceptual-motor, perceptual, and verbal skills were used. The problem here is that most investigators used only one or two tests to tap a given area of skill.^{14,16,22,45,50,55,57,58,63} Little or no attention was paid to the adequacy of the test in terms of whether it was a pure measure of the skill involved and whether the one or two tests that were used constituted a reliable and comprehensive assessment of the behavioral domain (e.g., motor functioning).

Finally, the precision of the dependent measures was also badly compromised in those investigations that used subjective behavioral measures without apparent concern for their reliability and/or validity. In several studies, behavioral checklists were used to rate subjects for behavior problems or hyperactivity, but no information was given about the content, reliability, or validity of these scales.^{55,57,65} In other studies, grades and school records of behavior ratings done by teachers were utilized in spite of the fact that such measures are known to be highly subjective and are influenced by the biases of the teacher toward a given student.^{52,57}

Frequent flaws were found in these studies with respect to their design and choice of statistical procedures. Many of the research design problems in the current literature have arisen because studies have relied on traditional control vs. experimental group designs in which one dependent measure is examined at a time. The use of this approach assumes that the experimental and the control groups are "comparable" in all respects except their exposure to lead. In this case, variables such as age, sex, socioeconomic status, educational level of the parents, parental rearing styles, and a history of pre- and/or postnatal complications are known to have an effect on behavioral development. However, the accurate measurement and experimental control of such concomitant variables has not always been adequate.

A better approach to studying multiple dependent and independent variables relies on statistical procedures which are called *multivariate analyses*. These can be used to determine whether or not there is a statistically significant relationship between lead level and behavioral measures when factors such as age, sex, socioeconomic status, etc. are held constant. Only a few studies in the literature have used these procedures.^{51,51b,61}

While the fact that most studies do not use multivariate statistics is an important liability even within the experimental vs. control group approach, the execution of the studies has been less than outstanding. Problems involved with the measures used to identify experimental and control subjects often badly compromised the execution of these studies. These problems have already been detailed elsewhere in this overview. Therefore, this discussion will be limited to adequacy of the control procedures instituted to insure the comparability of the two groups on all variables except lead exposure.

Problems frequently occurred with procedures used to match groups. Matching can be done on either a pair-by-pair basis or by matching groups on the average value of concomitant variables. A group match would be sufficient when subjects are fairly homogeneous on correlated variables like race, SES, age, and educational level. However, when the subjects vary a great deal on these dimensions, pair matches would seem to better insure the equal distribution of these factors across each group. In some of the studies reviewed, group matches were made even though the subjects varied widely in some of these factors.⁵² For example, it is possible that children from higher SES families could have been found more often in the experimental or in the control group, thus possibly biasing the findings. Paired matches would have avoided this problem. On the other hand, there were studies which apparently used no matching, even though the investigators made it clear that there were wide differences between subjects in terms of SES, housing, and neighborhood.^{52,65} In these cases one has no idea at all as to the comparability of the two groups.

Another problem with matching arose when investigators failed to foresee and insure the comparability of the groups on what later turned out to be some critical variables. One major difficulty in this regard involved the use of socioeconomic status as a summary measure of the family's rearing style, attitudes toward education, etc. The assumption that class membership uniformly determines family structure, rearing styles, and social values is probably not valid. Hence, the use of measures of social class may be too gross to precisely measure critical differences in the child's social environment. For example, parent-child relationships, which play a significant role in the development of children either by themselves or in conjunction with environmental factors like lead exposure, would not be adequately assessed with a global measure like SES. Similar problems arose regarding matters of relocation or attrition of study subjects. In some studies, families in the control groups often relocated in newer housing.^{52,55,57,58} The investigators assumed that children living in new housing were not exposed to lead and that differences between the "exposed" and "not exposed" groups could be interpreted as being due to lead exposure. However, they failed to recognize that the families that relocated may have been those in which the parents were the most concerned about the health and the cognitive and social stimulation of their children. These factors, rather than exposure to lead, might account for the differences between the groups. In the same vein, there occurred a loss of subjects, usually controls, because they moved out of the neighborhood, often to better housing and school districts.^{52,55,57,62} It is possible that such attrition was most prevalent among families who were more concerned about the welfare and education of their children. This might have resulted in a downward bias of intellectual and perceptual motor skills in the remaining control subjects, thus minimizing differences found between the

groups. Yet, there does not seem to have been any effort made to determine if attrition biased or changed the composition of the groups.

In closing, some mention should be made about the misapplication of statistical procedures that occurred in these studies. The use of multiple "t"-tests and the application of statistical tests to only portions of the control and experimental distributions are the major problems of a statistical nature that were encountered in these studies. With regard to the former, many studies tested their findings by utilizing 10 to 15 separate "t"-tests. This procedure, as has repeatedly been pointed out, inflates the chance of obtaining a significant "t" value by chance alone.⁷² It is more appropriate to first apply an overall test of significance between the groups either by using an analysis of variance technique or, in cases where the sampling and the data dictate, a nonparametric form of statistical analysis that would accomplish the same task. Specific comparisons can then be made in cases where the foregoing statistical analysis indicates significant differences between the groups are present in the data. In the latter case, using only part of the data (typically the "tails" of the distribution) may lead to erroneous claims of significant differences between the groups. Such procedures again inflated the chances of obtaining statistical difference by ignoring the majority of the data.

C. Conclusions and Recommendations

A total of 22 studies were reviewed which addressed the question of the effects of moderate lead exposure on the behavioral development of children. The results from these studies are quite equivocal. There was no clear trend indicating that moderate lead exposure caused any abnormalities in behavioral development in children nor was there any compelling evidence which suggested that this was not the case. Sixteen studies looked for behavioral irregularities as a result of moderate exposure. Of these, six found results favoring such an effect,^{49, 51b, 55, 57, 58, 62} eight failed to find any such effect,^{44, 48, 51, 53, 54, 59-61} and two yielded findings which were quite ambiguous with respect to this issue.^{50, 52} A further complication with respect to these studies is that many of them had methodological deficiencies which undermined the credibility of their results, be they in a positive or a negative direction with respect to lead effects. There were an additional six studies^{63, 65, 67, 68, 70, 70a} which sought confirming evidence of a relationship between moderate lead exposure and behavioral abnormalities like mental retardation which were already present in the children. All six of these studies obtained positive results, but again all of them had methodological flaws which weakened the validity of their findings.

The contradictory nature of the studies reviewed also appears if one simply considers those five studies which, in the reviewer's opinion, were the soundest in terms of methodology and execution.^{49, 51, 51b, 60, 61} In this case two of these studies found results in a positive direction,^{49, 51b} and three found results in a negative direction.^{51, 60, 61} In summation, the findings from all 22 studies appear to be contradictory and do not offer any resolution to the question of whether or not moderate lead exposure is a significant health hazard. The data reviewed do not permit unequivocal determination of the level at which lead exposure begins to constitute a significant health hazard as reflected in impaired neurobehavioral development.

Some reviewers, most noticeably the 1977 EPA air lead document,⁷⁵ have suggested the trends for a moderate lead effect can be seen if one combines positive findings from well-controlled studies with those studies showing borderline (p-values between 0.10 and 0.20) effects. The arguments for accepting less stringent p-values are that lead poses a potentially serious health hazard and that one might expect that the effects of low to moderate lead exposures on human behavioral development would be subtle and hard to demonstrate. The reviewer acknowledges that there might be some merit

in accepting borderline findings in an area of concern such as this, but one also has to recognize and weigh the possibility that doing this may increase the risk of making a type-I error; that is, attributing significance to differences that were due to chance.

The argument that one might expect the effects of low to moderate lead exposure to be subtle is a reasonable one. However, one should not confuse small effects (for example, a 2- or 3-point decrease in the IQ scores of lead-exposed children) with subtle effects. Small changes in test scores may not, in and of themselves, signify that lead has affected the day-to-day functioning of these children at home, in the neighborhood, or at school. By contrast, so-called subtle effects signify less obvious losses that seriously impair the day-to-day behavior of the children involved. In this sense, subtle should refer not to small, significant differences in test scores, but rather to losses in skills such as attention span or impulse control. Though not typically felt to be as important as intelligence or social behavior, these very skills are known to exert a strong influence on intelligence and personality. Low to moderate lead exposure may indeed cause subtle effects on behavior, but the present literature has failed to describe such effects. Investigators have yet to thoroughly examine behavioral skills that could subtly undermine intellectual and/or social behavior.

Finally, the judgment of trends in the data has to rest, to some degree, on the particular reviewer's evaluation of the methodological quality of each study. A review of the evidence suggests that the majority of studies in this area contain flaws which obscure a clear interpretation of their findings.

It should be apparent that the ideal course that needs to be taken in this area of research is to prospectively monitor lead exposure and behavioral development in large samples of children. Prospective studies are more difficult and time consuming, but it would appear that this is the best and most efficient manner of addressing the question of the neurobehavioral effects of moderate lead exposure and at the same time avoid many of the problems that are so abundant in the current literature. Ideally, serial measures of internal exposure (e.g., blood-lead levels) should be taken at 3- to 6-month intervals up through at least the end of the third year of life, if not through age 4 or 5. Again, ideally, one should obtain exposure histories in a sample or samples of children who can be expected to vary over the full range of exposure, starting with children with almost no likelihood of exposure to lead and ending with those who might be expected to show prolonged exposure to lead at the upper levels (50 to 60 $\mu\text{g}/\text{dl}$) of the asymptomatic range. This kind of careful and persistent monitoring of lead exposure should enable the investigators to more appropriately approach the controversial question of whether or not moderate lead exposure affects behavioral development in children. If this question is answered in the affirmative, this same kind of design, and only this kind of design, will put investigators in the position of identifying whether there are certain ages when children are more vulnerable to asymptomatic lead poisoning and whether there are different neurobehavioral effects in children caused by variations in the duration and/or the dosage levels of lead exposure.

A second recommendation applies to the area of behavioral assessment. In this case, careful attention needs to be paid to developing and using a number of tests to tap discrete behavioral functions that mediate intellectual and social behavior. A rigorous neuropsychological approach to assessing behavioral functions should be adopted in studies as the best way of insuring measurement of areas of skill where deficits due to moderate lead exposure are likely to occur. This means developing thorough measures of visual perception, fine motor skills, auditory comprehension skills, etc. This would also include direct and more specific measures of activity level and of personal-social functioning. For subjects 5 years of age or above, much of this task development has already been done since these children are old enough to be evaluated on the Indiana Reitan Neuropsychological Test Battery, a measure that has already been shown to

specifically and broadly assess the neuropsychological status of children of this age. Direct measures of activity level⁷³ and objective measures of personal-social functioning are also readily available.⁷⁴

Behavioral assessment is much more difficult in studies involving children under the age of 5. Yet by all accounts this is the most critical age group to study. Thus, a great deal of preliminary work must be done in terms of devising measures to use on infants and toddlers that will assess their neurobehavioral status. To some degree, the Bayley Scales and the McSCA are useful in this regard. However, there is a growing body of experimental literature on groups of atypical infants (e.g., Down's Syndrome infants) suggesting some techniques that may be sensitive to early CNS damage. Among these are measures of orienting, habituation, visual preference, and infant memory that were described in an earlier section. Other tasks measuring developing hand use, learning, and infant and toddler cognition are potentially useful as part of a battery of tests designed to examine the neurobehavioral effects of moderate lead exposure in the birth through 5-year age range.

A final recommendation would be for investigators to adopt multivariate research designs in approaching the study of this problem. This recommendation carries with it the proviso that investigators pay careful attention to assessing "control" variables if they are going to make adequate use of such designs. This should include pertinent information on the child's birth and health history. It should also include direct measures of such social variables as mother-child interaction and parental attitudes toward rearing children. Careful measures of these control variables should be entered into a multivariate analysis with two purposes. One would be to test the relative effects of lead on the neurobehavioral development of children when the effects of these other potent and naturally co-occurring variables are statistically controlled for in the data. The second purpose would be to see whether the neurobehavioral effects of moderate lead exposure differ under varying social and/or health conditions. In other words, is moderate lead exposure of a given dose and duration more damaging to a child who has a poor health history or to a child growing up malnourished and emotionally neglected than it is to a child in good health and/or from a home where parents are concerned about his or her well being?

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